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Utilization Of Lung Cancer Screening And Molecular Testing To Improve Lung Cancer Outcomes

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UTILIZATION OF LUNG CANCER SCREENING AND MOLECULAR TESTING TO IMPROVE LUNG CANCER OUTCOMES

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DEDICATION

To my mother, Nancy Ersek Suttles, who allowed me to choose my own path but always made sure I chose wisely.

To those diagnosed with lung cancer, may you never lose hope.

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ABSTRACT

Despite progress in detection and treatment, lung cancer remains the leading cause of cancer-related death in the United States. The United States Preventive Services Task Force (USPSTF) recommends adults at high risk for lung cancer undergo annual low-dose computed tomography (LDCT) screening, however, lung cancer screening (LCS) uptake remains low. Qualitative research on family physician (FP) perceptions and experiences with LCS has been limited since USPSTF publication and Centers for Medicare and Medicaid Services (CMS) decision memo. We conducted a qualitative study to assess FP knowledge and perceptions of LCS and gain insight into their current experiences with LDCT. A convenience sample of FPs were asked to participate in Skype audio interviews. A semi-structured interview guide was used to navigate the interviews. A theme codebook was developed using the constant comparison technique. All interviews were coded by two reviewers.

We found that FP knowledge about the scientific evidence and patient eligibility criteria for LDCT was suboptimal. Age and smoking history were the primary drivers of a FPs decision to discuss LCS. Most FPs knew that they should initiate LDCT discussions with high risk patients, however, they indicated that they would be willing to screen patients outside of the specified criteria. LDCT cost and lack of time were cited as barriers. Facilitators included screening tools in the clinic waiting room and electronic medical record notifications. These results indicate a need for FP education about LCS, as well as tools to assist providers in the clinic.

As LCS becomes more widely adopted, more lung cancers will be detected at an earlier stage. While tumor molecular testing (MT) is currently recommended for patients with metastatic disease, MT could increasingly be used in early stage patients to guide initial treatment decisions. Disparities in MT and targeted therapy utilization may exist. We quantitatively evaluated factors related to MT and erlotinib utilization and the impact of these on overall survival (OS).

Stage IIIB/IV non-small cell lung cancer (NSCLC) cases diagnosed between January 1, 2002 and December 31, 2012 and available through the South Carolina Central Cancer Registry were linked to SC State Employee Health Plan (SCSEHP) and Medicaid administrative claims data. MT and erlotinib utilization were independently categorized as "yes" or "no" based on claims data. We found several characteristics associated with MT, including younger age, having an out-of-state provider, being diagnosed in 2010 or later, adenocarcinoma histology, and low tumor grade. Risk of death was reduced and OS was longer for patients with MT. Younger age, female sex, SCSHEP insurance, having an out-of-state provider, adenocarcinoma histology, and having molecular testing were associated with erlotinib utilization. Risk of death was lower for patients treated with erlotinib and OS was longer. These results suggest that tumor MT and erlotinib utilization lead to improved patient survival. Additional research should evaluate these important factors in nationally representative datasets.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I:

INTRODUCTION

Statement of the Problem

In the United States, an estimated 1,688,780 new cases of cancer will be diagnosed in 2017.[1] Of these, approximately 222,500 cases of lung cancer will be diagnosed and an estimated 155,870 individuals will die from the disease.[1] In North Carolina and South Carolina, collectively, 12,261 new cases are estimated (NC: 7,940; SC: 4,321) and deaths are estimated.[1] Lung cancer is the second most frequently diagnosed cancer and is the leading cause of cancer mortality among both males and females, with five-year survival rates of 18% among all races.[1] Over half (57%) of cases are diagnosed with distant disease, meaning the patient has advanced or metastatic disease at the time of diagnosis.[1] Only 22% of cases are diagnosed with localized or regional disease.[1] Five year survival is better for those diagnosed with local disease (54%) compared to those with regional or distant disease (27% and 4%, respectively).[2]

Since 1990, a decrease in the lung cancer mortality rate has been observed in both males and females, but the decline has been greater for males.[1] Hopefully, this decreasing trend will remain stable or improve in future decades, as improvements in lung cancer detection and treatments are made. Lung cancer screening with low-dose computed tomography (LDCT) and treatment with molecularly targeted therapies are two approaches to the control of lung cancer in the United States, both of which have become

popularized within the last two decades. The goal of LDCT is to identify lung cancer in earlier stages, when the disease is more treatable, while the goal of molecularly targeted treatment is to improve survival and quality of life (QOL).

This dissertation will consist of three lung cancer research manuscripts. The first will focus on family physician (FP) lung cancer screening perceptions and practices (Chapter IV). The second and third manuscripts will focus on: 1) factors related to molecular testing and its impact on survival (Chapter V); and 2) factors related to utilization of erlotinib and erlotinib's impact on survival (Chapter VI).

Lung Cancer Background

Lung cancer is among the most commonly diagnosed cancers and is the number one cause of cancer death among adults in the United States.[1] Broadly, lung cancer can be divided into two subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC can be further sub-categorized as adenocarcinoma, squamous, or large cell carcinoma. NSCLC is the most common type, comprising 85% of cases. A new lung cancer screening approach, low-dose computed tomography, allows for detection of early stage lung cancer that can be curable[3]. For patients diagnosed with early stage NSCLC, surgical resection is the cornerstone of their treatment, however, approximately 70% of patients diagnosed with NSCLC present to the clinic with late stage disease.[1] Patients with late stage NSCLC experience widespread disease and surgical resection alone is not sufficient. Historically, the treatment of metastatic NSCLC has relied heavily on platinum-based doublet chemotherapies with a meager median overall survival of ~8 months and low response rates of approximately 20%.[4]

Advances in the molecular profiling of lung tumors have led to the discovery of many molecular abnormalities, which has led to a more personalized approach to lung cancer treatment, especially for those patients whose tumors are of the adenocarcinoma subtype. Molecular testing can identify patients whose tumors do not harbor clinical actionable alterations and who are unlikely to respond to targeted drug therapies, sparing these patients and payers the cost of non-efficacious therapy. For those patients whose tumors do have clinically actionable molecular abnormalities, targeted drug therapies, such as *EGFR* tyrosine kinase inhibitors (TKIs) and *ALK* inhibitors, are FDA approved and are the preferred treatment. Patients with *EGFR*-mutated lung cancers who received targeted therapies in clinical trials have experienced significant improvements in tumor response rates (RR) and median progression-free survival (PFS) and have experienced fewer side effects and an improved quality of life.[5-9] While PFS has been favorable for patients receiving targeted drugs, increased overall survival (OS) has not been observed in patients participating in clinical trials[10-12] possibly due to drug crossover in randomized studies.[10] Still, use of targeted therapies is considered by the National Comprehensive Cancer Network (NCCN) as the best choice to treat patients with advanced NSCLC whose tumors harbor molecular abnormalities.

Specific Aims

Study 1. Family Physician Perceptions and Experiences with Low-Dose Computed Tomography Screening for Lung Cancer

Recently, new guidelines for lung cancer screening using low-dose computed tomography (LDCT) have been published by the United States Preventative Services Task Force (USPSTF) and supported by many professional cancer societies and advocacy

groups, such as the American Cancer Society, American Society of Clinical Oncology, American College of Radiology, and National Comprehensive Cancer Network (Table 1.1). As a result, the Centers for Medicare and Medicaid Services (CMS) approved coverage for annual lung cancer screening using LDCT in select, high risk adults. Since the announcement of the CMS coverage decision memo and publication of requirements for reimbursement on February 5, 2015 (Table 1.2),[13] qualitative literature published on family physician perceptions and experiences towards LDCT has been sparse.[14,15] Quantitative data previously collected and published was obtained through the administration of an electronic and paper questionnaire from family physician members of the South Carolina Chapter of the American Academy of Family Physicians[16] and primary care physician employees at Carolinas HealthCare System[17] and was used to inform the development of an interview guide for this study. Follow-up interviews were conducted with a subset of physicians who completed the questionnaire and who agreed to be contacted for future research to obtain qualitative data. The specific aims of this qualitative study are to:

1. Assess family physician knowledge surrounding the current scientific evidence on LDCT for lung cancer screening
2. Assess family physician knowledge with regards to current patient eligibility criteria defining patients at "high risk" for lung cancer
3. Explore family physician attitudes on implementation of lung cancer screening discussions, including shared decision-making processes
4. Explore barriers and facilitators to lung cancer screening
5. Explore current LDCT referral and follow-up practices

Study 2. Factors Predicting Molecular Testing and Erlotinib Utilization and their Impact on Survival in Patients with Advanced, Non-Small Cell Lung Cancer

State and national cancer registries do not collect data on the molecular characteristics of lung tumors. Thus, it has been difficult to evaluate the public health significance of molecular testing and targeted therapies at a population level. Specifically, utilization of molecular testing, factors associated with receipt of testing, and survival of patients with NSCLC undergoing molecular testing and treatment with targeted therapies has not been previously evaluated at the population level across the time period evaluated in this study. This study will use an administrative claims database linked to a state cancer registry database to examine these topics. In this study, 2002-2014 data from South Carolina (SC) Central Cancer Registry NSCLC cases will be linked to SC State Employee (SCSEHP) and SC Medicaid members to examine these topics at the state level. Knowledge on utilization and factors associated with molecular testing and erlotinib use can give us insight to the current landscape o across SC and can allow us to identify factors associated with non-utilization.

Published research on the utilization of molecular testing and erlotinib in patients with NSCLC at the population level across these years is extremely limited. Research addressing lung cancer molecular testing and erlotinib utilization in the US and their impact on survival has not previously been conducted using SC linked administrative claims and cancer registry data. By combining administrative claims data with population-based cancer registry data, we have the advantage of being able to capitalize on the strengths of each dataset while minimizing their weaknesses when used alone. For example, SCCCR does not collect data on whether or not a patient had molecular testing,

but this information is available by searching for molecular testing Common Procedure Terminology (CPT) codes in SCSEHP and Medicaid claims. The results of this study will characterize the current landscape of molecular testing in NSCLC patients and identify disparities in utilization among SC residents. Increasing the number of patients who receive molecular testing (and when appropriate, targeted therapy) can lead to decreases in the cost of supportive care that would result from treating chemotherapy toxicity and may lead to increased quality of life for more patients. Additionally, it may also spare chemotherapy in patients that are unlikely to benefit.

The specific aims of this study are to:

1. Identify factors that are associated with molecular testing and erlotinib utilization
2. Estimate propensity scores for each case to predict molecular testing and to predict erlotinib utilization
3. Evaluate the relationship between molecular testing and survival
4. Evaluate the relationship between erlotinib utilization and survival

Significance

Lung cancer screening with low-dose computed tomography is underutilized and most lung cancers are diagnosed late-stage.

Historically, lung cancer screening methods in the US have included chest x-ray, computed tomography, and sputum cytology, however, no mortality benefit was observed with any of these approaches. Recently, the National Lung Screening Trial reported a 20% reduction in lung cancer mortality and a 6.7% reduction in overall mortality with annual screening using LDCT for three years.[18] Because of these findings, the United States Preventative Services Task Force recommended LDCT screening for high

risk patients at the grade B level in 2014.[19] A grade B level recommendation requires lung cancer screening to be provided free of charge to patients covered under the Affordable Care Act. Subsequently, the Centers for Medicare and Medicaid Services (CMS) announced coverage for high risk adults defined as those aged 55–77 years who are asymptomatic for lung cancer, have a tobacco smoking history of at least 30 pack-years, are current or former smokers (quit within the past 15 years) and have documentation of a counseling and shared decision-making visit prior to LDCT screening.[13]

Currently, about 70% lung cancers are diagnosed late or advanced stage (III or IV).[20] Of these, roughly 40% have metastatic disease and despite surgery or combined therapy are considered incurable, while about 40% have locally advanced disease and will undergo multimodal therapy.[21] Lung cancer screening with LDCT can identify earlier stage lung cancer that is more likely to be treated with surgical resection alone.

Median overall survival in NSCLC patients is low with chemoradiation.

Multiple treatment modalities exist for lung cancer patients. Surgical resection, systemic chemotherapy, and radiotherapy are the cornerstones of lung cancer therapy. However, surgical resection is mostly limited to those presenting with early stage disease. Most unresectable, advanced stage patients are treated initially with one of four platinum doublet chemotherapy regimens (e.g., cisplatin plus paclitaxel or docetaxel, cisplatin plus gemcitabine, or carboplatin plus paclitaxel)[21] with concurrent radiation therapy (if tolerable), as this combined approach has yielded the best overall survival.[20,22] An Eastern Cooperative Group (ECOG) evaluation of these four regimens was recently conducted in 1,207 patients, of which 1,155 were eligible for analysis. The median

overall survival was 7.9 months (95% CI: 7.3-8.5), with no meaningful difference in survival by chemotherapy regimen. One and two-year survival rates were 33% and 11%, respectively (95% CIs: 30-36% and 8-12%, respectively). More recently, the ECOG evaluated overall survival of the drug pemetrexed (a folate antimetabolite) versus carboplatin plus pemetrexed.[23] In this randomized trial of 205 eligible patients, a small increase in overall survival was observed in the carboplatin-pemetrexed group (median OS = 9.3 months, 95% CI: 7.4-11.2 months) with a more favorable toxicity profile.[23] Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has also emerged as a therapeutic drug in the treatment NSCLC. In a multicenter, phase II study, patients treated with paclitaxel-carboplatin plus bevacizumab (PCB) combination therapy had significantly better overall survival compared to those treated with paclitaxel-carboplatin (PC) alone, although an increase in treatment-related deaths was observed. Median OS for those on the PCB arm was 12.3 months compared to 10.3 months on the PC arm (HR=0.79; P=0.003).[24] While chemotherapy does have its place in the treatment of NSCLC patients, newer drug therapies, including targeted therapies and immunotherapies, are quickly emerging as efficacious treatment modalities.

Clinically relevant molecular abnormalities have been identified in patients with NSCLC.

Within the past one to two decades, knowledge of molecular markers has proliferated. The three most studied clinically relevant molecular abnormalities in NSCLC include Kirsten rat sarcoma viral oncogene homolog (*KRAS*), epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*), and these abnormalities are typically mutually exclusive.[20,25] However, other molecular abnormalities also exist (i.e. *MET*, *ROS-1*).[25-27] This dissertation focuses on molecular testing in general and

focuses on the utilization of the *EGFR* TKI, erlotinib (Tarceva; Genentech). *EGFR* is a cell surface receptor that is activated either by protein overexpression, increased gene copy number or genetic mutation. *EGFR* is involved with cell proliferation, suppression of apoptosis (cell death), cell motility, invasion and angiogenesis (formation of new blood vessels).[20,25] Prevalence of *EGFR* mutated lung cancers range from 15%-80%, depending on racial and behavioral characteristics. Those most likely to have *EGFR* mutated lung tumors include Asian ethnicity, females, never smokers, and those with adenocarcinoma histology.[25] The *RAS* family mutations (including *KRAS*) encode for proteins on the cells surface and are involved with cell proliferation, survival, and metastasis.[20] In adenocarcinoma patients, prevalence of *KRAS* mutated lung cancers ranges from 20%-30%, with higher prevalence among Caucasians and ever-smokers.[20,25]

The availability of molecular tests to predict response to targeted therapies is increasing.

Molecular testing can be conducted using both FDA-approved tests ("companion diagnostics") and other non-FDA approved laboratory developed tests. Some tests are run individually, while some are run as a "panel" and may assess multiple biomarkers in one test administration (e.g., Lung Cancer Panel, Solid Tumor Mutation Panel by Next Generation Sequencing). Local Coverage Determinations published by Medicare administrative contractors are used to establish Medicare coverage guidance for existing and newly developed laboratory diagnostic tests. Historically, clinical laboratories have billed payers, such as Medicare, using a technique call "code stacking". This method-based approach to billing uses combinations of CPT or Healthcare Common Procedure Coding System (HCPCS) codes to bill for molecular tests. This approach can result in a variety of code combinations, as well as costs, for one molecular test.

As the availability of molecular testing has increased, the need for distinct, individualized, gene-specific codes emerged. Revisions to the coding systems were drafted and a new set of CPT codes were published in 2013 that are more accommodating to the modern molecular testing performed in laboratories. For example, Palmetto GBA, the administrative servicer for South Carolina's Medicare program, has approved the code 81235-22 (EGFR, common variant) for EGFR testing of tumor and plasma specimens.[28]

Molecular testing is used to assist providers in selecting targeted therapies based on tumor characteristics and these therapies have yielded improved outcomes.

Several targeted therapies have been approved by the FDA to treat patients with NSCLC whose tumors harbor *EGFR* mutations, including the *EGFR* TKIs erlotinib, afatinib, and gefitinib. Improvements in progression-free survival and overall response rates have been noted.[6,29] Additionally, targeted drug therapies are less toxic than systemic chemotherapy regimens and studies have reported low frequencies of both adverse events (e.g. skin reactions, diarrhea, and appetite challenges) and serious adverse events.[6,29,30]

TABLES

Table 1.1 Professional societies that support the use of lung cancer screening with low-dose computed tomography

	USPSTF	ACS	ACCP/ ASCO	AATS	ALA	NCCN	CMS
Population	55 to 80 years 30 pack year smoking history Current or have quit in past 15 years No symptoms	55 to 74 years 30 pack year smoking history Current or have quit in past 15 years No symptoms In good health	55 to 74 years 30 pack year smoking history Current or have quit in past 15 years	55 to 79 years 30 pack year history OR 20 pack years (with additional lung cancer risk factors)	Should follow that of the NLST, USPSTF, CMS	55 to 74 years 30 pack year smoking history and smoking cessation with 15 years OR Age ≥50 years with ≥ 20 pack year smoking history plus one additional	55 to 77 years 30 pack year smoking history Current or have quit in past 15 years No symptoms Written order for lung cancer screening

						risk factor for lung cancer (other than secondhand smoke exposure)	
Smoking cessation	Yes	Yes	Not discussed	Not discussed	Yes	Yes	Yes
Shared decision making	Yes	Yes	Not discussed	Not discussed	Yes	Yes	Yes
Year Updated	2013	2015	2012	2012	2015	2015	2015

Abbreviations: AACP-American College of Chest Physicians, AATS-American Association for Thoracic Surgery, ACR-American College of Radiology, ACS-American Cancer Society, ALA-American Lung Association, ASCO-American Society of Clinical Oncology, CMS-Centers for Medicare and Medicaid Services, NCCN-National Comprehensive Cancer Network, NLST-National Lung Screening Trial, USPSTF-U.S. Preventive Services Task Force.
*Note: USPSTF is grade B recommendation. NCCN is a category 2B recommendation.

Table 1.2. Requirements for CMS Coverage of LDCT Screening for Lung Cancer

Initial Screening	
Age	• 55-77 years
Symptoms	• None; asymptomatic patients only
Tobacco smoking history	• ≥30 pack years
Current smoking status	• Current or former smokers; former smokes must have quit within the last 15 years
Health Care Professional	• Physicians or qualified non-physician practioners (physician assistants, nurse practioners, clinical nurse specialist (as defined by Section 1851(r)(1) of the Social Security Act))
Shared decision-making visit	• Determination and documentation of age, lack of signs/symptoms of lung cancer, calculation of smoking pack-years, and report of current smoking status • Use of 1+ decision aids that describe the benefits and harms of screening • Counseling on the importance of adhering to LDCT screening schedule (annual LDCT), impact of comorbidities, and agreement to undergo diagnosis and

	treatment if suspicious findings are present • Written order for LDCT for lung cancer screening • National Provider Identifier (NPI) for ordering practioners
Radiology imaging facility	• Performs LDCT with volumetric CT dose index of ≤3.0mGy for standard size patients and appropriate reductions/increases for smaller/larger patients • Uses standardized lung nodule identification, classification, reporting system • Provides information and interventions for smoking cessation in current smokers
Reading radiologist	• Board certified/eligible with American Board of Radiology (ACR) or equivalent organization • Documented diagnostic radiology and radiation safety training and continuing medical education (according to ACR standards) • Involvement in supervision/interpretation of at least 300 chest CTs within past 3 years • Conduct LDCT screening in a radiology facility that meets CMS eligibility criteria

Lung cancer screening registry	• Radiology facility must collect/submit data to CMS-approved registry for each LDCT screening performed. Minimum data submission includes: facility identifier, NPI, patient identifier, CT manufacturer/model, indication for screening, nodule identification system employed, patient smoking history, radiation dose delivered, screening date • Establishment of steering committee/governance board to oversee registry • Registry management plan with identification of key registry personnel • Operation plan describing plan for collecting and submitting data to the registry and from registry to CMS, including agreement to use CMS-approved data dictionary • Registry catchment area and list of facilities participation in the registry • Description of methods to permit linkage of registry data to external databases (e.g. Medicare claims) • Description of data management, quality review and validation • Quality assurance plan

Subsequent Screenings	
Health Care Professional	• Physicians or qualified non-physician practioners (physician assistants, nurse practioners, clinical nurse specialist (as defined by Section 1851(r)(1) of the Social Security Act))
Shared decision-making visit	• Not required, however if practioners decides to conduct a lung cancer screening shared decision-making visit, the same requirements as the initial screening apply

*Adapted from Centers for Medicare and Medicaid Services Decision Memo (February 2, 2015).[13]

CHAPTER II:

LITERATURE REVIEW

Low-Dose Computed Tomography for Lung Cancer Screening

Historical Summary of Lung Cancer Screening

For over 60 years, research has been conducted on the efficacy of various lung cancer screening methods, including chest radiography, sputum cytology, and low-dose computed tomography, but until recently, no recommendation was made as to which method, if any, increased lung cancer survival. In the 1950s, the earliest clinical trials in the United States and London evaluated chest x-ray, sputum cytology, or the combination of both and were usually evaluated at six month intervals. These early trials had major limitations including lack of randomization and control groups. In the 1970s, the National Cancer Institute (NCI) sponsored three randomized controlled trials, specifically aimed at examining mortality from lung cancer. These trials were conducted at Johns Hopkins University (JHU), the Mayo Clinic, and Memorial Sloan-Kettering Cancer Center (MSKCC). Each trial had a slightly different design and the goals was to evaluate the efficacy of sputum cytology. At JHU and MSKCC, both the intervention and control groups received annual chest x-rays and the intervention group received chest x-ray plus sputum cytology screening every four months. At the Mayo Clinic, the intervention group received chest x-ray and sputum cytology every four months and while the control group received these services annually. This trial was designed to evaluate the effect of the frequency of screenings. Overall, the results of these NCI-sponsored trials showed

that screening detects earlier stage lung cancers and that case-survival rates were improved however, mortality rates did not differ. Additionally, these trials suffered from length-time, lead and patient selection bias, common biases of screening studies.[31] Other studies conducted around the same time period in Czechoslovakia and Germany had similar results.[32,33] As a result of these studies, in 1989, neither the American Cancer Society, the American College of Radiology, the National Cancer Institute, the United States Preventive Services Task Force, or the Canadian Task Force recommended any screening test at any frequency for lung cancer.[34]

Observational, Single Arm Studies Involving Low-Dose Computed Tomography

Advances in multidetector helical computed tomography resulted in better scan images with decreased radiation exposure.[35] Other advantages include increased scan speed, improved spatial resolution, and a clearer detection of lung nodules due to the cross-sectional data display.[36] During the 1990s and early 2000s single arm, observational studies demonstrated improved identification of lung nodules and early-stage lung cancers[37] with low-dose helical computed tomography. Also during this time, the Prostate, Lung, Colorectal, and Ovarian (PLCO) began and completed enrollment to assess mortality benefit for lung cancer screening using chest x-ray compared to usual care.[38] Ultimately no mortality benefit was established,[38] confirming the need for research on other lung cancer screening methodologies.

Studies such as the Early Lung Cancer Action Project (ELCAP) and the International Early Lung Cancer Action Project (I-ELCAP), both initiated in 1993, were instrumental in reporting not only the benefits of LDCT in terms of increased nodule detection, but also demonstrated that screening with LDCT detected smaller and more

lung nodules compared to chest radiograph[39] and that LDCT screening led to the detection of cancers that could be cured.[3] The I-ELCAP reported that 85% of cancers detected by LDCT lung cancer screening were classified as clinical stage I and the estimated 10-year survival was 88%.[3] A similar trial was conducted in Japan among 1,611 asymptomatic patients ages 40-79 years. The Anti-Lung Cancer Association (ALCA) study reported that 71% of cases at initial screening were Stage IA and 82% of cases at diagnosed at repeat scan were stage IA.[40] Many other single arm studies of LDCT were conducted during this time period (Figure 2.1).[40-50] Trials such as these ultimately lead to the development of several large, randomized clinical trials of LDCT in the United States and Europe.

Randomized Clinical Trials Involving Low-Dose Computed Tomography

The Lung Screening Study (LSS) was a feasibility study evaluating the use of LDCT versus chest x-ray (CXR). A total of 3,318 subjects participated in the study. Eligible subjects were between 55 and 74 years old, had at least a 30 pack-year history of cigarette smoking, and were either a current smoker or a former smoker (if former, had to have quit within last 10 years).[51]

Any non-calcified nodule ≥4mm found during screening was considered a positive screen. A total of 25.8% of LDCT and 8.7% of CXR scans were positive at the baseline scan and 48% and 40% of cases were diagnosed as stage I cancer, in the LDCT arm and CXR arm, respectively. This study was the first to demonstrate that a randomized clinical trial evaluating LDCT was feasible in the United Sates and ultimately led to the development of the National Lung Screening Trial (NLST).[51]

In 2002, the United States launched a larger, randomized trial comparing annual LDCT to CXR.[36] The NLST, sponsored by the National Cancer Institute (NCI), enrolled 53,454 "high risk" subjects ages 55-74 with a 30 pack-year history of cigarette smoking, who were current or former smokers. Former smoker must have quit within the past 15 years.[18] Subjects were randomized to either three annual LDCT scans or three annual CXR scans. Across all three rounds of screening, there was a higher rate of positive screening tests with LDCT compared to CXR (T0, 27.3% vs 9.2%; T1, 27.9% vs 6.2%; T2, 16.8% vs 5%).[18] A high proportion of positive screening tests were followed up with further diagnostic evaluation (90%), such as additional diagnostic imaging and more invasive procedures (thoracotomy, bronchoscopy, needle biopsy), at T0 compared to the other time points. Across the three rounds, a high proportion of the positive screening tests were false-positives (96.4% LDCT; 94.5% CXR). Despite a high number of false-positives resulting in additional follow-up, the majority of patients had no complications resulting from the additional procedures (99.6% LDCT; 99.7% CXR). Among those with at least one complication, rates were similar or higher for the LDCT arm compared to the CXR arm for all complications assessed. The most striking result from this trial was the reduction in lung cancer mortality observed with LDCT, 20% (p=0.004). Additionally, the rate of all-cause mortality was reduced by 6.7% with the use of annual LDCT (p=0.02). For the first time, lung cancer screening, using LDCT, resulted in a mortality benefit.

The Nederlands Leuvens Longkanker Screeningsonderzoek (NELSON) study is the largest LDCT screening trial conducted in Europe. Starting in 2003, subjects aged 50-75 years old, who had smoked either ≥15 cigarettes a day for ≥25 years or ≥10

cigarettes per day for ≥30 years, and who were current or former smokers were enrolled. Former smokers must have quit within the past 10 years. The original study design called for three screening rounds (baseline, 1 year later, 2 years later, 2.5 years later) included 15,822 subjects, mostly males. The goal was to demonstrate a 25% reduction in the risk of lung cancer death with LDCT compared to no screening 10 years after randomization.[52,53] However, a fourth round was added in 2009 (5.5 years later) to evaluate the inclusion of a 2.5-year screening interval (n=7,915).[54] Over the first three screening rounds, 493 positive LDCT scans were reported and of these 40.6% were diagnosed with lung cancer. Of these lung cancer cases, 70.8% of lung cancers were diagnosed as stage I and 8.1% were diagnosed as stage IIIB/IV.[53] Most subjects were diagnosed with adenocarcinoma (51.2%). In the fourth screening round, more patients were diagnosed with late-stage lung cancer (17.3%, p=0.02) and squamous-cell (21.7%), bronchoaveloar (8.7%), and small-cell carcinomas (6.5%) compared to the second round of screening (p=0.001).[54]

A recent randomized trial conducted in the United Kingdom compared a single screen LDCT to standard care in high risk patients.[55] Individuals age 50-75 years old and residing specific geographic areas were identified through population Primary Care Trust records and were asked to complete a questionnaire to identify those at high risk of lung cancer. High risk patients were defined as those who scored a 5-year lung cancer risk of ≥5% on the Liverpool Lung Project version 2 risk model.[56] Those who were deemed high risk were asked to participate in the United Kingdom Lung Screening (UKLS). Of the 249,988 who were identified through Primary Care Trust records, 4,061 consented to participate in the UKLS trial and were randomized to one of the two arms. Of the 1,994

individuals who received a LDCT screen, 34 (1.7%) were diagnosed with lung cancer at baseline. A total of 47.7% of participants underwent at least one additional screen due to a nodule finding on the baseline scan, resulting in a total of 42 diagnosed lung cancers. The majority of diagnosed lung cancers were adenocarcinomas (59.5%). A total of 85.7% of the diagnosed cancers were stage I or II and 83% had surgery as their primary treatment. Mortality reports on this data are expected in coming years.[55]

The NLST and NELSON studies are the largest performed to date. Other randomized clinical trials of LDCT include the Danish Lung Cancer Screening Trial (DLCST),[57] ITALUNG,[58] Lung Cancer Screening Intervention (LUSI),[59] and the Multicentric Italian Lung Detection (MILD).[60]

Risks and Benefits of Lung Cancer Screening with Low-Dose Computed Tomography

Proponents of lung cancer screening with LDCT argue that the benefits of screening justify its use, however, most agree that, as with many screening tests, there are some inherent risks. False positive scans are one such risk[61] and are perhaps the leading concern for screening. False positive scans also contribute to the overall cost of screening. The false-positive screening rate in most studies involving LDCT is high. For example, in the NLST, the false-positive rate for LDCT was 96.4%, but this was only slightly higher than the false-positive rate for CXR (94.5%).[18] Inclusion of the Lung-RADS classification (introduced in May 2014) reduced the false positive rate but also slightly reduced test sensitivity.[62] The Lung-RADS classification changes the criteria for a positive screen slightly. The definition of a positive screen using Lung-RADs includes a 6-mm transverse bidimensional average (20mm for nonsolid nodules) and requires

growth for preexisting nodules as opposed to the NLST, which required only a 4-mm greatest transverse diameter.[62]

Conversely, another harm of lung cancer screening is false negatives. There may be instances where a lung cancer is not detected on a screening test and may give patients a sense of "protection" from lung cancer and false reassurance.

Overdiagnosis is a common risk of any cancer screening program including lung cancer screening with LDCT.[61,63,64] Overdiagnosis can occur when a patient is diagnosed with an indolent or slow growing cancer that would not otherwise have been detected without screening. Persons may in fact die of other reasons without ever being diagnosed. The USPSTF modeling study reported a 10-12% of screen-detected cancer cases are overdiagnosed.[19]

Another risk of lung cancer screening is increased exposure to radiation.[61,64,65] Persons undergoing LDCT screening may be exposure to additional radiation, not only at the time of LDCT screening, but also at screening follow-up. For a LDCT the average effective dose value is about 2 mSv for an average size patient compared to 7 mSv for a standard CT.[66] Brenner *et al* evaluated the estimated risk of lung cancer due to radiation exposure from screening. If 50% of current or former smokers ages 50-74 residing in the United States received annual LDCT screening, the estimated number of lung cancer cases would increase by 1.8% (95% CI: 0.5 – 5.5%).[65] Excess risk of radiation-induced lung cancer is greatest for those around 55 years of age.[65] Unfortunately, this corresponds to the appropriate age range for lung cancer screening. Increased risk for radiation-induced lung cancer depends on age at start of screening, how many scans a

person has, and other sources of radiation exposure.[19] One scan is not the concern; it is the cumulative amount of radiation that is concerning.

Discovery of incidental findings on a lung cancer screening LDCT present another potential harm of screening. A NELSON sub-study found a non-clinically relevant incidental finding (e.g., emphysema, thyroid nodule) rate of 73% and a possibly clinically relevant incidental finding (e.g., liver lesion, aortic aneurysm > 6 cm) rate of 8% (of which 79% were actually clinically relevant after further evaluation).[67] A report of 2,812 patients by Gareen *et al* reported a significant incidental finding (e.g. abdominal aortic aneurysms and renal cysts) rate of 12.2%. While some studies report that incidental findings are commonly picked up by LDCT screening, the USPSTF stated there was insufficient evidence on harms of incidental findings identified through LDCT screening.[19]

Lastly, complications resulting from diagnostic work up procedures[68,69] may also present a potential harm to persons undergoing screening with LDCT. Following a positive screening, a person may need to undergo additional follow-up, such as additional CT imaging or needle biopsy, which may present additional harm. Overall, the NLST reported few and minor complications arising from diagnostic evaluations following a positive screen (1.6% in the LDCT arm).[18] In the NLST, risk of major complications following surgical procedures for benign nodules was 4.5 per 10,000 for the LDCT arm compared to 1.5 for the CXR arm.[69]

Benefits of lung cancer screening with LDCT include reduction in risk of lung cancer and all-cause mortality, psychosocial benefits, such as reassurance of having a

normal CT scan, and the opportunity to incorporate smoking cessation into lung cancer screening decision making discussions.[68]

Cost of Lung Cancer Screening with Low-Dose Computed Tomography

A NLST cost-effectiveness analysis compared LDCT to no screening. Black *et al* reported that lung cancer screening with LDCT cost an additional $1,631 per person (95% CI: 1,557-1,709). LDCT provides an additional 0.0316 life-years per person (95% CI: 0.0154-0.0478) and 0.0201 quality adjusted life years (QALYs) per person (95%CI: 0.0088 - 0.0314). Incremental cost-effectiveness ratios (ICERs) were $52,000 per life-year gained (95% CI: 34,000 – 106,000) and $81,000 per QALY gained (95%: 52,000 – 186,000).[70] This amount is similar or less than other cancer screenings. The authors state that the cost effectiveness of screening will depend on how screening programs are implemented.[70]

Another study conducted by Mahadevia *et al* in 2003 simulated data to evaluate mortality and cost-effectiveness of LDCT compared to no screening for hypothetical cohorts of 100,000 current, quitting, and former heavy smokers aged 60 years while incorporating known screening biases and assuming 50% stage shift. Their simulated models revealed the cost-effectiveness of lung cancer screening with LDCT was $116,300 for the current smoker cohort, $558,600 for cohort of quitting smokers, and $2,322,700 for the former smoker cohort, respectively, per QALY gained.[71] Sensitivity analyses were also conducted to evaluate cost-effectiveness under a variety of efficacy assumptions. Age at first screening, stage shift, and length of follow-up were also varied. Under extremely ideal model conditions (e.g., lower probabilities for non-adherence, estimates for length and overdiagnosis bias, lower cost of LDCT screening, and better

QOL for localized stage), the cost-effectiveness of LDCT screening would drop to $42,500 per QALY for current smokers. Important to note, the simulated models did not include costs related to incidental findings.[71]

The UKLS trial described previously also included a cost effectiveness component. The ICER for single-screen LDCT screening was £8466 per QALY.[55] This translates to approximately $11,071, which is substantially less the found in the NLST, but differences in the frequency of screening in addition to resource expenses are likely to explain this difference.[55]

Physician Attitudes, Perceptions, and Experiences with Low-Dose Computed Tomography

Several studies have evaluated primary care physician attitudes, perceptions and practices regarding lung cancer screening with LDCT, prior to and following the publication of the NLST. The first quantitative study on primary care physician's lung cancer screening beliefs and recommendations was published in 2010.[72] Klabunde *et al* conducted a nationally representative survey of practicing PCPs from 2006-2007. A total of 962 physicians responded (70.6% response rate; 76.8% cooperation rate). Physicians were unsure of the USPSTF and American College of Radiology recommendations (38.8% and 58.2%). Overall, LDCT was perceived as a somewhat or very effective screening tool and was viewed as more effective than CXR or sputum cytology. Approximately 31% of the physicians believed that LDCT was effective in reducing lung cancer mortality.[72]

Physicians were also presented with clinical scenarios in which age, smoking history, and secondhand smoke exposure were varied. In cases where screening was

recommended, interestingly, physicians more frequently chose screening with CXR compared to LDCT or sputum cytology. Most physicians would screen the current smoker scenario (84.4%; CXR=40.1%, LDCT=17.2%). Few physicians reported that they would screen the age 50, never smoker (17.4%; CXR=16.5%, LDCT=0.2%).[72]

The first qualitative study, published by Henderson *et at* in 2011, conducted five telephone-based focus group with 28 primary care physicians (PCPs) in the United States to evaluate the factors influencing a PCPs decision to screen patients for lung cancer.[73] The focus groups were conducted in May and June 2009, prior to the publication of the NLST results. Physicians reported CXR as outdated and not sensitive enough to detect lung cancer. Some PCPs viewed CTs favorably stating that CT scans are efficacious and can detect small nodules. Most physicians were aware of the recommendations published by USPSTF and ACS. Some physicians reported using the recommendations to direct practice while others did not. Physicians who had multiple patients undergo follow-up for what turned out to be benign lesions had a negative view of lung cancer screening. Most physicians based their decision on whether to order lung cancer screening based on their perception of their patient's risk of lung cancer, however, the physician's perception of risk varied. Smoking was cited as the most important risk factor, however, other risk factors considered by physicians included family history, immunocompromised status, personal cancer history, secondhand smoke exposure, and history of pulmonary disease. Most physicians ordered a lung cancer screening test regardless of their knowledge of screening efficacy, when a patient requested the test.[73]

Physician practice regarding ordering lung cancer screening was also assessed. Just over two-thirds of physicians reported never ordering a lung cancer screening test,

while 55% ordered chest radiography and 22% ordered LDCT.[74] Almost 70% of physicians had at least one patient ask about lung cancer screening in the previous year. The authors noted that several factors influenced PCP ordering of LDCT. Time since graduating from medical school, being in a practice with 6-15 physicians, believing that at least one expert group recommended screening, recommending lung cancer screening for asymptomatic patients regardless of smoking exposure, and having patients ask about lung cancer screening all increased the odds of ordering LDCT.[74]

Approximately two years after the dissemination of the NLST results (2013), Lewis *et al* surveyed 293 PCPs (response rate = 60%) via email at a large academic medical center[75] to assess use of lung cancer screening, perceived screening effectiveness, knowledge of screening guidelines, perceived barriers to LDCT use and interest in screening education.[75] PCPs reported that the USPSTF, ACS, and ASCO guidelines influenced their practice (88.4%, 71.8%, 46.0%, respectively). Only 42% of PCPs viewed LDCT as very or moderately effective in reducing lung cancer mortality and 30% did not know about the benefit in reducing lung cancer mortality. PCPs who reported more than 15% of their practice consisting of current or former smokers and those who knew at least three of the guideline components (e.g., age, annual screening, start screening age of 50, end screening age of 75 or 80, 20 or 30 pack-year smoking history, and not including individuals exposed to only secondhand smoke) were more likely to perceive LDCT as very or moderately efficacious (OR=3.0, 95%CI: 1.1-8.4, OR=5.1, 95%CI: 2.6-9.9, respectively). Interestingly, colonoscopy, pap smear, and mammography had higher rates of perceived effectiveness (92.9%, 99%, 95.7%, all $p<0.0001$, respectively), while PSA had a lower rate (27.4%, $p=0.002$) compared to

LDCT.[75] Almost one-quarter of physicians reported using CXR to screen for lung cancer (21.3%, 95%CI: 16.0%-27.5%)[75], despite the results of the NLST reporting no mortality benefit with CXR by the time of this survey. Only 12.3% reported using LDCT (95%CI: 8.2%-17.5%). Knowing three or more guideline components significantly predicted likelihood of LDCT ordering (OR=3.0, 95%CI: 1.1-8.6). Most physicians (79.8%) were open to receiving further information and education on lung cancer screening.[75] Perceived major barriers to lung cancer screening reported by PCPs in this cohort included patient financial cost (86.9%), potential harm from false-positives (82.7%), patient knowledge (81.3%), potential patient harm, incidental findings requiring further workup (81.3.%), and insurance coverage/cost (80.1%).[75] Geographic availability, was also reported as a perceived barrier; approximately 25% of physicians reported geographic availability as a major or minor barrier.[75] A report by Eberth *et al* confirmed this perceived barrier and reported that while most LDCT screening centers were located in counties with the highest lung cancer incidence in the Northeast and East North Central states, in four states (Oklahoma, Nevada, Mississippi, and Arkansas) geographic availability of LDCT screening centers may be a concern.[76] A second study published by the Eberth team, surveyed members of the Society of Thoracic Oncology to determine availability of LDCT lung cancer screening programs. Fourteen states, including those where availability of LDCT screening centers was a concern, had no screening center respond to their survey.[77]

A qualitative assessment of PCP attitudes and beliefs occurred just prior to the Centers for Medicare and Medicaid services coverage determination announcement in 2015.[13] Hoffman *et al* conducted in depth, semi structured interviews with PCPs in New

Mexico clinics serving rural and urban minority patients from February-September 2014.[78] The interviews (n=10) focused on a range of lung cancer related topics, including tobacco cessation, perceptions of the NLST results, and perceptions and attitudes toward informed decision making for cancer screening. Prior to the interviews, physicians were given information on screening guidelines and results of the NLST. Some physicians were not aware of changes to screening lung cancer screening guidelines. No physicians reported ordering LDCT scans for lung cancer screening; however, some physicians reported ordering CXR and believed that this was in alignment with screening guidelines. No physicians reported a patient demand for LDCT services. Some providers were not aware of the NLST results. When presented information on the NLST, physicians perceived the absolute mortality risk to be small and were concerned about the high rate of false-positives and the risks of screening. Physicians also reported concerns over long term radiation exposure.[78]

PCPs reported being cautious to begin to offer LDCT screening in their clinics. Some PCPs stated that they would feel more obligated to offer screening if it were incorporated into performance measures. Additionally, some physicians reported concerns over whether New Mexico radiology facilities had the ability to support high quality screening programs and listed this a potential barrier. Other patient related barriers reported by PCPs included, travel expenses to get to a screening facility, as well as the costs of follow-up testing and potential treatment. Such costs would make screening for lung cancer unreasonable for their patients. Physicians were also concerned about the potential resource barriers they might face (e.g. time and effort), stating that PCPs are already overloaded and lack adequate time for preventive patient education.[78]

In addition to increased time required by physicians to conduct lung cancer screening visits, PCPs were also concerned about the responsibility of explaining such a complex screening test to their patients with limited appointment times and the low literacy of most patients. Physicians also voiced concern about discussing follow-up of abnormal findings with patients.[78]

A report by Volk and Foxhall published in August of 2015 surveyed 350 PCPs on their current lung cancer screening practices and readiness to implement lung cancer screening programs at two Continuing Medical Education events in late 2014 (following the USPSTF recommendation and draft CMS coverage decision memo).[79] Most PCPs reported being somewhat or very familiar with the current guidelines, however, only 10.1% had a formal lung cancer screening program in their practice. Over half (56.0%) planned to refer patients to high-quality screening programs, however, less than half were currently doing so (25.0% in practices that do not train residents; 43.1% in practices that offer residency programs). There were some concerns also reported. PCPs requested clarity on screening coverage, information on screening centers that offered LDCT, and decision aids and educational materials.[79]

A qualitative study by Kanodora *et al* assessed the perceptions and perspectives on lung cancer screening among Veteran's Affairs PCPs and patients.[15] A total of 13 PCPs in South Carolina participated in focus groups in 2014. PCPs at this site had participated in lung cancer screening programs since 2012. Their program consisted of clinical reminders built into the electronic medical records to notify VA PCPs that a patient was eligible, then the PCP made a referral to a lung cancer screening nurse coordinator for a shared decision-making visit. Posters, streaming videos, decision aids

in the clinic all facilitated conversations about screening. More than half aware of the PCPs were aware of USPSTF recommendations for screening, however there was variation in commitment and enthusiasm for LDCT. Additionally, some PCPs continued to believe CXR is effective.[15]

PCPs interviewed preferred that the lung screening nurse coordinator to review details with patients, like continued surveillance and the features of the scan (low-dose). The providers reported that a majority of patients willing to have screening, but some feared cancer diagnosis or other illness. Lung cancer screening discussions were met with little resistance and that resulted in shortened discussions, however, PCPs still reported not having enough time to have sufficient depth screening discussions. Only 23% of PCPs made referrals to local smoking cessation clinic and admitted to not devoting enough time to smoking cessation counseling.[15]

PCPs reported that patients with recent cancer deaths in the family or heavy smokers were more likely to request screening, but that they most often requested CXR. Some patients were concerned about exposure while in the military that may increase their risk for lung cancers.[15]

Another recent study, published in 2017 by Simmons et al, used focus groups consisting of Florida PCPs (e.g., physicians, nurse practioners, and physician assistants) to assess knowledge and attitudes towards lung cancer screening.[14] Prior to the focus group, PCPs were provided a summary of the current evidence for lung cancer screening, patient eligibility criteria, risks and benefits of screening, and reimbursement requirements in a webinar format. The majority PCPs stated that patients did not inquire about lung cancer screening and they were not recommending screening to patients. A

few reported still requesting CXR for screening purposes. The majority said they currently had limited information about screening, although most said they would recommend it if they had more information. Some providers also mentioned lack of understanding of the testing process and follow-up of abnormal results. After viewing the webinar on lung cancer screening, a few PCPs reported screening to be more complicated than they initially thought.[14]

Early detection was reported as the main benefit. PCPs also discussed that lung cancer screening discussions can motivate smoking cessation and overall outcomes. Others benefits included coverage for patients with insurance/Medicare, low-dose of radiation with the scan, and patient reassurance that they do not have cancer.[14]

The most common barriers to lung cancer screening were cost, time, and potential for false positives. The time barrier includes a simple lack of time to discuss, as well as concerns over the complexity of discussion required for the SDM reimbursement. Again, EMR pop-up reminders to indicated patient eligibility were viewed as facilitators to lung cancer screening.[14]

In the past couple years, several other quantitative assessments of primary care physician knowledge, perceptions, and utilization have been reported.[80-83] Earlier this year, Jemal *et al* reported extremely low rates of patient self-reported LDCT for lung cancer screening (<4%) between 2010 and 2015.[84] Despite these prior studies, research, education, and promotion of lung cancer screening is still of importance. Since the finalized CMS coverage decision memo was released in February 2015 and the use of CMS reimbursement codes for the shared decision-making counseling visit were

published, no mixed methods studies evaluating family physician perception and practices surrounding LDCT have been reported.

Molecular Testing in Non-Small Cell Lung Cancer

Over the last two decades, knowledge of the biology of cancer and the molecular pathways involved in cancer has flourished and a variety of treatments have been become standard, including targeted therapies and immunotherapies (Table 2.1). Identification of genetic anomalies, including mutations, gene rearrangements, and copy number changes, identified within cancer initiation and progression pathways have led to the development of personalized medicine and targeted therapeutics. Many lung cancer biomarkers have been researched and published however, only a few biomarkers for lung cancer have use in the clinic and directly impact patient treatment. Despite the clinical benefit of molecular testing and clinical guidelines for its use, molecular testing is likely still underutilized by thoracic oncologists, especially in the community-based setting[85].

Clinically Actionable Biomarkers for NSCLC

Several clinically actionable biomarkers have been identified in tumors of patients with NSCLC. For example, 15-25% of patients harbor KRAS mutations,[25,27] 3-7% harbor ALK fusions/translocations,[27,86,87] 2-5% harbor MET amplifications,[25,27] and 1-2% of patients have tumors that are ROS-1 rearranged.[25,27]

Among the most prevalent is the epidermal growth factor receptor (*EGFR*; also referred to as ErbB1). *EGFR* is a member of the ErbB family of receptors.[88,89] The *EGFR* signaling pathway is visualized in Figure 2.2. The most common *EGFR* abnormalities are point mutations and in-frame deletions.[90] Other abnormalities in *EGFR* include increases in gene copy number, *EGFR* single nucleotide polymorphisms (SNPs),

and *EGFR* protein expression.[91] *EGFR* is most frequently mutated in either exon 19 and 21 (L858R, L861Q) (Figure 2.3).[88] In exon 19, four amino acids are deleted. In exon 21, most commonly, a T to G mutation at nucleotide 2,573 leads to a substitution of arginine for leucine at position 585.[92] *EGFR* resistance mutations can also occur (exon 20 insertions and T790M).[93]

The *EGFR* mutation was first discovered in 2004 and is present in 10-35% of patients; it more frequently occurs in females and never smokers.[27,88,92,94,95] Incidence is higher in the Asian population; approximately 22-62% of East Asians with lung adenocarcinoma harbor *EGFR* mutations.[27,96,97]

EGFR testing is important for both predictive and prognostic implications. Presence of activating *EGFR* mutation indicates potential response to an *EGFR* TKI, such as gefitinib or erlotinib. Progostically, patients with *EGFR* mutations have better outcomes compared to patients whose tumors are *EGFR* wild-type.

Currently in the clinical setting, *EGFR*, *ALK*, and *ROS-1* are the most frequently used biomarkers to direct therapy and resistance mutations have emerged (e.g. *EGFR T790M*). A number of other mutations in lung adenocarcinomas exist, including *BRAF*, *KRAS*, *HER2*, *PTEN*, *MEK1*, *AKT*, *FGFR*, *c-MET* and *PIK3CA,*[22,26,95,98] however these mutations are not clinically actionable and are still under clinical investigation. Methods to molecularly profile tumors vary and include polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH), and chromatic in situ hybridization (CISH). Next generation sequencing (NGS) allows for assessment of multiple biomarker simultaneously and is the preferred approach to broad,

panel-based molecular profiling. Whole genome NGS provides the most comprehensive assessment of the tumor.[99]

FDA Approved Diagnostic Tests for EGFR Mutations

Several clinical assays are FDA approved for the detection of *EGFR* mutations, including the *EGFR* pharmDx, Therascreen *EGFR* RGQ PCR, and cobas *EGFR* Mutation Test.[26] These tests are performed using tumor tissue resected from the patient via biopsy or surgical resection. A blood-based *EGFR* test was also approved in 2016, cobas *EGFR* Mutation Test v2.[100] NGS, a broad molecular profiling approach, also has the ability to detect *EGFR* abnormalities.

Disparities in ordering molecular testing for lung cancer are likely to exist. A recent abstract presented at the ASCO Annual Meeting in 2014 revealed that academic oncologists were more likely than community oncologists to order a NGS molecular test (59.4% vs 33.4%, p=0.01).[101] Community oncologists are likely to be less knowledgeable and have less experience with NGS compared to their academic counterparts.[101]

Historically, billing for these tests was complex. There were no unique Current Procedural Codes (CPT) to test individual genes. Thus, laboratory billing managers billed by method of analysis (e.g. lysis of cells, extraction of highly purified nucleic acid) used to perform for the test in a technique called "code stacking". Code stacking results in different total costs depending on how each laboratory performs molecular testing and stacks the CPT codes. An example of three different *KRAS* testing code stacks is presented by Carlson and demonstrates a $35.98 difference in price depending on code stacking approach.[91]

To address this problem, the American Medical Association organized a workgroup to construct a new section of the CPT Pathology and Laboratory manual. The workgroup recommended a two-tiered, volume based coding format. Tests (including non-oncology) that are performed most frequently are assigned a Tier 1 level. Each tier has its own CPT code. At the time of publication of an article authored by Klein, 120 analytes and procedures were assigned to Tier 1 and 599 tests were placed into Tier 2 (9 levels). Each level had a CPT code used for that level. Test level is assigned based on the resources required to carry out the test. These new codes were published on January 1, 2013. The 2015 CPT edition now also includes sections for Multianalyte Assays with Algorithmic Analyses (MAAAs), Genomic Sequencing Procedures (GSPs), and Other Molecular Multianalyte Assays (for coding NGS).[102]

Clinical Practice Guidelines for EGFR Testing in Lung Cancer

Clinicians often rely on clinical practice guidelines (CPG) to direct and justify therapy. CPGs are systematically produced statements that guide practioners in decision-making throughout the healthcare spectrum, from preventive medicine to disease treatment and follow-up. Good CPGs present validity, reliability, reproducibility, clinical applicability, clinical flexibility, and clarity.[103] They consist of a multidisciplinary review process and document evidence for a particular procedure or treatment, as well as suggest areas for future research.[103,104] CPGs provide decision support tools that incorporate references and consider healthcare costs and coverage.[103]

By 2011, the National Comprehensive Cancer Network recommended the use of molecular testing in patients with brain, breast, colon, lung, and prostate cancers and acute myeloid leukemia[105]. The American Society of Clinical Oncology (ASCO) also

published a provisional clinical opinion (PCO) regarding the use of *EGFR* mutation testing for patients with advanced, NSCLC considering first-line treatment with an *EGFR* TKI, such as erlotinib or gefitinib.[104] The 2011 ASCO PCO reports that patients with *EGFR*-mutated NSCLC treated with *EGFR* TKIs have significantly higher rates of response and progression-free survival, however, no overall survival benefit from the selection of patients for *EGFR* testing had been observed at that point. They based their opinion on the results of five clinical trials of gefitinib and erlotinib. At the time of publication and currently, the clinical opinion is that patients with non-squamous NSCLC who are being considered for first-line therapy with an *EGFR* TKI should have their tumor evaluated for *EGFR* mutations to guide therapy decisions.[104]

Around the same time, a consensus meeting of Asian and Canadian medical oncologists, pulmonologists, and molecular pathologists also produced a standardized *EGFR* mutation testing protocol.[91] They recommended that Asian patients with non-squamous, NSCLC, particularly adenocarcinoma, be routinely tested for *EGFR* mutations. Testing in patients with squamous histology may be considered, except for males and heavy smokers, but is not recommended. Their report also included detailed laboratory considerations and methodologies and asks the pathology community to consider the emergence and growth of multiple biomarker tests, as done in the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination Trial (BATTLE).[91,106,107]

In 2013, a joint guideline was released by the College of American Pathologies (CAP), International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology (AMP).[103] The purpose of this guideline was to describe the

evidence-based recommendation for lung cancer molecular testing required to guide treatment with both *EGFR* and ALK-targeted therapies. A total of 37 guideline recommendations were made. Major recommendations included the emphasis on testing for *EGFR* mutations and ALK fusions in all patients with advanced, lung adenocarcinoma (including those with mixed subtypes), regardless of sex, race, smoking history, or other clinical risk factors. *EGFR* testing was not recommended in squamous or large cell carcinomas. The consensus group also prioritized *EGFR* and ALK testing over other molecular tests. The group recommended that *EGFR* testing be conducted at the time of diagnosis for patients who present with advanced stage disease and at time of recurrence or progression for those who initially presented with earlier stage disease and were not previously treated. The guideline also included information on specimen sample quality, processing, testing validation, and result reporting.[103] The European Society of Medical Oncology (ESMO) largely agrees with the previously described guidelines for *EGFR*-mutated NSCLCS in its metastatic NSCLC guideline.[108] The ASCO officially endorsed the guideline issued by the CAP/IASLC/AMP team in 2014.[109,110]

Epidemiologic Studies Evaluating EGFR Testing in Lung Cancer Patients

Few studies evaluating the utilization of molecular diagnostic testing, specifically *EGFR* testing, in a population-based setting currently exist. In a retrospective, observational study published in 2013, several proprietary and publicly available datasets were merged to evaluate hospital use of the *EGFR* assay among lung cancer patients.[85] Multivariate logistic regression was performed to identify factors associated with a hospital's use of the assay. A total of 7,958 *EGFR* tests were ordered from 743

institutions. Non-federal acute care hospitals ordered the largest proportion of *EGFR* tests (76%). Geographically, California, Florida, Illinois, New York, and Pennsylvania hospitals ordered the highest number of tests. Interestingly, North Dakota (a state with no National Cancer Institute (NCI) Cancer Center or hospital with cytogenetic testing accreditation) had the highest percentage of lung cancer cases tested (17.6%). However, these hospitals had academic medical school affiliations, participated in NCI cooperative group studies, were located in urban areas, and had above average education and income.[85]

In the multivariate models, affiliation with an academic medical center (OR=1.48; 95% CI:1.20-1.83), participation in NCI cooperative group studies (OR: 2.06; 95% CI: 1.66-2.55), ability to perform PET scans (OR: 1.44; 95% CI: 1.07-1.94), located in a metropolitan county (OR: 2.08; 95% CI: 1.48-2.91) and above average education and income (OR: 1.46; 95% CI: 1.09-1.96 and OR: 1.46; 95% CI: 1.04-2.05, respectively) were significantly associated with ordering molecular tests.[85] Annual number of lung cancer cases, inpatient chemotherapy, and race were not related to assay ordering.

Pan *et al* assessed *EGFR* biomarker testing using US Oncology data from the iKnowMed™ database, billing claims, and chart reviews.[111] Of 26,381 patients with existing or newly diagnosed non-squamous NSCLC, 1,168 met the additional eligibility criteria, which included, but was not limited to, only those patients diagnosed with stage IIIB/IV disease and who initiated second-line therapy between January 1, 2007 and June 30, 2011. Few patients received testing for *EGFR* (11.0%) prior to date of initiation of second-line therapy. When the analysis was restricted to only those whose index date was prior to 2010, the rate of patients was only 2.3%. In 2010, the *EGFR* testing rate

significantly increased to 15.2% in 2010 ($p<0.0001$) and increased again to 32.0% in the first six months of 2011 ($p<0.0001$). Half of patients with *EGFR*-mutated NSCLC were treated with erlotinib-containing regimens.

Another US study assessed the real-world patterns of *EGFR* testing in the population-based setting.[112] Enewold and Thomas used Surveillance, Epidemiology, and End Results (SEER) database to identify a random sample of patients diagnosed with NSCLC and conducted a National Cancer Center Patterns of Care (POC) study. Eligible patients included those diagnosed in 2010 with invasive, histologically confirmed, primary NSCLC. Patients with a history of cancer, diagnosed with a second cancer (within 60 days), diagnosed at autopsy or death certificate, those with neuroendocrine carcinomas, those with unknown stage, and those younger than 20 years old were excluded. The medical records of sampled patients were reviewed and the physicians of sampled patients were queried using POC survey instruments.[112]

A total of 1,358 patients diagnosed with NSCLC were included in the analyses. The majority of patients were stage III (18.2%) or stage IV (55.3%). Overall, 16.8% of patients with NSCLC had *EGFR* testing performed. More adenocarcinomas were tested than other histologies (20.8%). *EGFR* testing was also more frequently performed in patients with stage IV disease (19.9% for all histologies; 22.6% for adenocarcinoma), however, no statistically significant differences were found by stage. Of all patients with an *EGFR* mutation, 33.6% received erlotinib, while 48.3% of stage IV patients with an *EGFR* mutation did. Factors significantly associated with *EGFR* testing in stage IV patients included Hispanic and Asian Pacific Islander heritages ($p<0.01$), married status ($p=0.05$), having private, military, or other insurance ($p<0.01$), non-smoker status

(p=0.04), adenocarcinoma or other non-specified carcinoma histology (p<0.01), having no comorbidities(p<0.01), and living at least two months post-cancer diagnosis (p<0.01).

In 2017, two epidemiologic studies of *EGFR* testing in NSCLC patients were published. One study, conducted by Shen *et al*, used data from Truven Health MarketScan (commercial health plans and Medicare supplemental plans) from patients diagnosed between January 2013 and June 2014,[113] while the study by Lynch *et al* used Veterans data from patients diagnosed between 2011 and 2013.[114] Both of these studies assessed *EGFR* testing only, not broad molecular testing.

In the study by Shen *et al*, 18% of included all NSCLC patients (overall cohort) had a claim for *EGFR* testing within 6 months of diagnosis. Increasing rates of *EGFR* testing were observed over time, 16%-21% over the study period. When limited to adenocarcinoma histology, this increased to 37%. When limited to patients who received the drug erlotinib, the testing rate was 42%. Mean time from diagnosis to *EGFR* testing was 40 days. In the overall cohort, patients who were younger, female, residing in the western region of US, and had lower comorbidity scores were more likely to receive *EGFR* testing.[113] This population-based assessment of *EGFR* testing indicates that *EGFR* testing rates in the US are still low, despite recommendations by oncology groups supporting its use.

Lynch *et al* also reported subpar rates of *EGFR* mutation testing in their population of Veterans.[114] Approximately 34% of patients who were eligible for EGFR testing had testing performed. The majority of patients tested had adenocarcinoma histology. In 7% of the tested cases, *EGFR* sensitizing mutations were detected, which is much lower than the reported average in the US (10-15%). As EGFR mutation tends to

develop in non-smokers, this finding is expected. Veterans have a higher smoking rate compared to the general US population.

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Overview of FDA Approved Targeted Therapies for EGFR-mutated NSCLC

EGFR mutations can be treated with both monoclonal antibodies (e.g., cetuximab) and tyrosine kinase inhibitors (TKIs).[27] Three *EGFR* TKIs are FDA approved for use in *EGFR*-mutated NSCLC, gefitinib, erlotinib, and afatinib (Figure 2.4). One *EGFR* TKI, osimertinib, is only approved for patients whose tumors were *EGFR*+ (exon 19 and 21 L858R) and developed resistance.

Gefitinib (IRESSA) was the first to receive FDA approval (accelerated) for lung cancer treatment in unselected populations in 2003,[92] however, its approval was later withdrawn from the market due to failure to reach clinical efficacy endpoints in confirmatory trials.[115] The drug's manufacturer later designed and executed clinical trials of gefitinib in selected (*EGFR*-mutant) patient populations with greater success and gefitinib was approved for use in patients whose tumors harbor *EGFR*+ (exon 19 and 21 L858R) mutations in the US in 2015. The administration of gefitinib in patients is contingent upon use of a companion diagnostic to identify the required mutations (therascreen *EGFR* RGQ PCR Kit).[116]

Afatinib was approved in the US in 2013.[117] Afatinib (Gilotrif) is indicated for use as first-line therapy in patients whose tumors harbor *EGFR* (exon 19 and 21 L858R) mutations. Afatinib was approved for use with the companion diagnostic test therascreen *EGFR* RGQ PCR Kit.[117]

Erlotinib (Tarceva), some would say, has dominated the US *EGFR* TKI market in recent years, first gaining approval in 2004 for the treatment of unselected patients with locally advanced or metastatic NSCLC after failure of one prior chemotherapy regimen.[118] Erlotinib also received approvals in 2010 and 2013, for maintenance therapy and for first line treatment in the selected, *EGFR*-positive (exon 19 and 21 L858R), respectively. Patients must undergo *EGFR* testing with erlotinib's companion diagnostic test, the cobas *EGFR* Mutation Test.[119]

Randomized Phase 3 Clinical Trials Involving Erlotinib

Multiple preclinical and early phase (I and II) trials of erlotinib have been conducted globally.[120-125] Randomized phase III trials evaluating response rate (RR), progression-free survival (PFS), and overall survival (OS) have also been conducted internationally, in various settings and patient populations (Table 2.2). In selected patient subgroups, RR and PFS have mostly been increased with erlotinib, however, trials assessing OS have reported mixed results.

Second line and beyond

The first FDA approval for the use of erlotinib in the second-line setting and beyond was based on data from the BR.21 study published by Shepherd *et al.*[11] The randomized, placebo-controlled, double blind trial evaluated erlotinib (150 mg) versus placebo following failure of first-line or second-line chemotherapy. OS, PFS, overall response rate (ORR), duration of response, toxicity, and quality of life were assessed. Eligible patients included those who met the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-3, pathological evidence of NSCLC, recovered from chemotherapy side effects, no prior breast cancer, melanoma, or

hypernephroma, no symptomatic brain metastases, no clinically significant cardiac disease within past 12 months, no ventricular arrhythmias and no clinically significant ophthalmologic or gastro-intestinal abnormalities. Patients were not required to have *EGFR*-mutated NSCLC. A total of 731 patients were randomized to erlotinib (n=488) or placebo (n=243).[11]

Overall response rate (partial and complete responses) was better in the erlotinib arm (8.9%) compared to the placebo arm (<1%; p<0.001). Response rate (RR) for patients with *EGFR*-positive tumors was 11.3% compared to 3.8% for patients with *EGFR*-negative tumors (p=0.10). Duration of response was also better for the erlotinib arm compared to placebo (7.9 vs 3.7 months (mos), p<0.001, respectively). Additionally, PFS and OS was improved for the erlotinib arm compared to placebo. Progression-free survival was 2.2 vs 1.8 months (Hazard ratio (HR): 0.61, p<0.001). Overall survival was 6.7 vs 4.7 months (HR: 0.70, p<0.001).[11] After adjustment for treatment and other significant factors, adenocarcinoma subtype (HR: 0.8, 95%CI: 0.6-0.9, p=0.004), Asian origin (HR: 0.7, 95% CI: 0.5-0.9, p=0.01) and never-smoking status (HR: 0.8, 95% CI: 0.6-1.0, p=0.048) were significant predictors of survival. Toxicities (rash and diarrhea) and quality of life were acceptable with erlotinib therapy.[11]

Subset analyses of patients from the BR.21 study assessed the role of *EGFR* protein, copy number and mutation status in response and survival outcomes[126]. Female sex (p=0.007), Asian origin (p=0.02), never smoker status (p<0.001), adenocarcinoma subtype (p<0.001), and polysomy or amplification of *EGFR* (p=0.03) were associated with response. Increased response to erlotinib for patients with *EGFR*- mutated tumors compared to patients with *EGFR* wild-type tumors was observed, however the difference

in response between the groups was not significant (16% vs 7%, p=0.37). OS was not influenced by *EGFR* expression, copy number or mutation status.[126]

Another study that evaluated erlotinib in the second line setting was published by Garassino *et al* in 2013.[127] The TArceva Italian Lung Optimization tRial (TAILOR) trial assessed the efficacy of erlotinib compared to the standard second-line chemotherapy, docetaxel, in patients with *EGFR* wild-type NSCLC tumors. The primary endpoint was overall survival and secondary endpoints included PFS, RR, and QOL. Patients included in the trial were those who failed previous chemotherapy (pemetrexed, vinorelbine, gemcitabine), were not previously treated with taxanes or anti-*EGFR* drugs, and had ECOG PS of 2 or less.[127]

A total of 222 patients were randomly assigned to received either erlotinib (n=122) or docetaxel (n=110). Tumor response in the erlotinib group was not longer than the docetaxel group (3.0 vs 15.5 months (mos), p=0.003). Median PFS was 2.4 months in the erlotinib group compared to 2.9 months in the docetaxel group HR:0.71, 95% CI: 0.53-0.95, p=0.02). Median OS was shorter in the erlotinib arm compared to the docetaxel arm (5.4 vs 8.2 mos, HR=0.73, 95% CI: 0.53-1.00, p=0.05). The results of this study demonstrate that treatment with docetaxel is preferred to erlotinib in the second-line, *EGFR* wild type setting.[127]

The Tarceva in Treatment of Advanced NSCLC (TITAN) study was conducted concurrently with the SATURN maintenance therapy study.[98] However, unlike SATURN (which included patients without disease progression), the TITAN study enrolled patients who rapidly progressed on standard chemotherapy (within four cycles). Eligibility criteria were similar to that of the SATURN study, with the exception that

TITAN also included ECOG PS 2 patients. The primary endpoint of this randomized, international trial was OS. RR and OS were also assessed. There were no statistically significant differences in RR, PFS, or OS. The results of the TITAN study were not impressive, however, the study suffered from multiple limitations (e.g., underpowered, unbalanced baseline factors progostically benefiting the chemotherapy arm).[98]

A Greek randomized study by Karampeazis *et al* evaluated erlotinib compared to pemetrexed in the second line and beyond setting.[9] The primary endpoint of this trial was time to progression (TTP), and RR, PFS, and OS were evaluated as secondary endpoints. Biomarker status was also assessed. Eligible patients included those who were diagnosed with stage IIIB/IV NSCLC with a ECOG PS of 0-2, were pemetrexed and TKI-naïve, and progressed after one or two lines of chemotherapy. Those patients with second primary tumors, active infections, severe heart disease and uncontrolled diabetes were excluded.[9]

A total of 179 patients were randomized to the erlotinib arm; 178 were randomized to receive pemetrexed. RR was better for the pemetrexed arm compared to the erlotinib arm (11.4% vs 9%, p=0.469). PFS and OS did not differ significantly between the pemetrexed and erlotinib groups (2.9 vs 3.6 mos, p=0.136 and 10.1 vs 8.2 mos, p=0.986, respectively). There were no differences in RR or OS by *EGFR* mutation status.[9]

First line combination therapy

A phase III trial of erlotinib evaluated the drug in combination with standard chemotherapy (carboplatin and paclitaxel) in the first-line setting.[128] The primary objective of the TRIBUTE trial was OS. Other objectives included time to progression (TTP), ORR, and safety. PFS was not assessed. Eligible patients include those with histologically confirmed stage IIIB or IV NSCLC with ECOG PS of 0-1. Patients with

prior systemic chemotherapy, symptomatic or untreated brain metastases, unstable disease that would preclude use of chemotherapy, and inadequate laboratory values were excluded. *EGFR* protein expression was not an eligibility requirement. Patients were randomly assigned to receive daily erlotinib plus chemotherapy concurrently (n=539) or placebo plus chemotherapy concurrently (n=540).

There was no significant difference in objective RR, TTP, or OS in the TRIBUTE trial. Objective RR for the erlotinib plus chemotherapy arm was slightly higher compared to the placebo plus chemotherapy arm (21.5% vs 19.3%, p=0.36). Median OS was similar between the arms (HR:0.995, 95% CI: 0.86-1.16, p=0.95). In a subgroup analysis, the only group to demonstrate a survival advantage with the addition of erlotinib to standard chemotherapy was in never smokers. Never smokers who received erlotinib plus chemotherapy survived longer compared to those who received placebo plus chemotherapy (22.5 vs 10.1 mos, HR=0.49, 95% CI:0.28-0.85). Never smokers who received erlotinib also had an increased TTP compared to the placebo group (6.0 vs 4.3 mos, HR=0.50, 95% CI: 0.31-0.80). Rash, diarrhea, and nausea were higher in the erlotinib arm.[128]

Erlotinib was also evaluated in combination with chemotherapy (cisplatin and gemcitabine) in the first line setting in the Tarceva Lung Cancer Investigation Trial (TALENT).[129] TALENT was an international study designed to evaluate OS, TTP, RR, duration of response, and QOL. Eligible patients included those with histologically confirmed, unresectable, locally advanced, recurrent, or metastatic NSCLC (stage IIIB/IV) with EGOG PS of 0-1, and adequate laboratory values. Patient with previous exposure to chemotherapy/systemic antitumor therapy or *EGFR* directed agents were

excluded. Patients with unstable systemic disease, other prior malignancies (within 5 years), and significant ophthalmologic abnormalities were also excluded.[129]

Of the eligible patients, 1,159 were randomly assigned and started study therapy. Patients received either erlotinib plus chemotherapy (cisplatin and gemcitabine) or placebo plus chemotherapy for six cycles. RR was similar between the two arms; 31.5% of patients responded to treatment with erlotinib plus chemotherapy and 29.9% responded to treatment with placebo plus chemotherapy. There was no difference in OS survival between the arms (43 vs 44.1 weeks (wks); HR=1.06,95% CI: 0.90-1.23, p=0.49). *EGFR* expression (by IHC) was not correlated with response or survival outcomes.[129]

First line monotherapy

Following positive RR, PFS, and OS results with erlotinib in the second-line and beyond setting,[11] several studies evaluated the drug as monotherapy in the first-line setting.[7,12,130] The first trial to evaluate erlotinib in the first-line monotherapy setting was conducted by Zhou *et al* in China.[7] The purpose of the OPTIMAL trial was to evaluate the efficacy (RR, PFS) and tolerability of erlotinib versus standard chemotherapy (carboplatin/gemcitabine). The open-label, randomized trial included patients with histologically confirmed stage advanced or recurrent IIIB/IV NSCLC with activating *EGFR* exon 19 deletion or exon 21 L858R point mutation. Other eligibility criteria included presence of measurable disease, EGOG PS of 0-2, and adequate laboratory values. Patients with uncontrolled brain metastases and those who had received previous systemic therapy for advanced cancer were excluded.[7]

A total of 165 patients were randomized (83 to erlotinib arm; 82 to standard chemotherapy arm). 83% of patients on the erlotinib arm achieved a complete or partial

response compared to 36% for the standard chemotherapy arm (p<0.0001). Median PFS was significantly better for patients treated with erlotinib compared to patients treated with standard chemotherapy (13.1 vs 4.6 mos, HR=0.16, 95% CI: 0.10-0.26, p<0.0001). OS data were not mature at time of publication. Erlotinib administration was associated with a higher incidence of skin rash and diarrhea, but were low in severity (73% vs 19%, p<0.0001 and 25% vs 6%, p=0.00085, respectively).[7]

Also in the first line, monotherapy setting, the EURTAC trial, conducted in France, Italy, and Spain by Rosell *et al*, evaluated the safety and efficacy of erlotinib compared to standard platinum-based chemotherapy (cisplatin/docetaxel or cisplatin/gemcitabine; carboplatin was allowed for patients unable to tolerate cisplatin).[12] Inclusion criteria included histologic confirmation of stage IIIB/IV NSCLC, measurable/evaluable disease, and no history of chemotherapy for metastatic disease. Only patients with activating *EGFR* mutations (either exon 19 deletion or exon 21 L858R mutation) were enrolled. Additionally, patients with asymptomatic, stable brain metastases were allowed. Patients were randomized in a 1:1 fashion to receive either erlotinib (n=86) or standard chemotherapy (n=87). Trial endpoints included RR, PFS, OS and safety. 64% of patients treated with erlotinib achieved a response compared to only 18% in the standard chemotherapy group. Median PFS was significantly longer in the erlotinib arm compared to the standard chemotherapy arm (9.4 vs 5.2 mos, HR=0.42, 95% CI: 0.27-0.64, P<0.0001). OS did not differ significantly between the two arms (19.3 mos for erlotinib vs 19.5 mos for standard chemotherapy, HR=1.04, 95% CI: 0.65-1.67, p=0.87). Common side effects included anemia and neutropenia.[12]

Following the positive interim analysis, the trial was halted and full data analysis was conducted. A slight increase in PFS was observed in the erlotinib arm compared to the standard chemotherapy arm (9.7 vs 5.2 mos, HR=0.37, 95%CI: 0.25-0.54, p<0.0001). FDA approval for use of erlotinib monotherapy in the first line setting was based on the results of the EURTAC trial. Updated RR, PFS and OS data are included in the erlotinib package insert. RR continued to be better for the erlotinib group compared to the standard chemotherapy group. PFS remained better for the erlotinib group compared to the standard chemotherapy group (10.4 vs 5.2 mos, HR=0.34, 95% CI: 0.23-0.49, p<0.001), however, there also remained no significant difference in OS (22.9 vs 19.5 mos, HR=0.93, 95% CI: 0.64-0.35).[131]

Lee *et al* evaluated erlotinib as first line monotherapy therapy in the TOPICAL trial.[130] Conducted in the UK, this randomized, placebo-controlled trial evaluated efficacy (RR, PFS, OS), toxicities and quality of life. Patients included in the trial were those with stage IIIB/IV newly diagnosed, pathologically confirmed NSCLC who were chemotherapy naïve, and deemed unsuitable for chemotherapy due to performance status ≥2. Patients were not required to have *EGFR* mutations. The treatment arms were slightly imbalanced with 350 patients treated with erlotinib and 320 patients receiving placebo.[130]

Response rate was better in the erlotinib group compared to the placebo group (4% vs 2%). A small, but significant improvement is PFS was observed with first line erlotinib monotherapy compared to placebo (2.8 vs 2.6 mos, HR=0.80, 95% CI: 0.68-0.93, p=0.0054). No difference in OS was observed (3.7 vs 3.6 mos, HR=0.92, 95% CI: 0.78-1.07, p=0.31). Cognitive and physical functioning was better in the erlotinib arm.

Interestingly, a subgroup analyses of first-cycle rash revealed improved PFS and OS for those in the erlotinib arm who had rash compared to those who did not have rash (HR=0.24, 95% CI: 0.16-0.35, p<0.0001).[130]

Maintenance therapy

Erlotinib has also been evaluated as maintenance therapy. The Sequential Tarceva in Unresectable NSCLC (SATURN) trial evaluated the administration of erlotinib as switch maintenance therapy in an international study.[132] The objectives of this study were to evaluate PFS in patients with both wild-type and *EGFR*-mutated tumors. Patients with histologically confirmed, measurable unresectable or metastatic NSCLC with EGOG PS of 0-1 were included. Other eligibility criteria included lack of previous exposure to anti-*EGFR* agents, uncontrolled, symptomatic brain metastases, or other malignancies within past 5 years. Finally, patients were only eligible if they had participated in the run-in phase of the study and had not progressed following first-line platinum based doublet chemotherapy (investigators choice of seven regimens).[132]

Tumor response rate was better with erlotinib compared to placebo (11.9% vs 5.4%, p=0.0006). Median PFS was longer in the erlotinib group compared to placebo (12.3 vs 11.1 weeks, HR=0.71,95% CI: 0.62-0.82, p<0.0001) in the overall population and was also prolonged in the *EGFR*-mutant population (12.3 vs 11.1, HR=0.69, 0.58-0.82, p<0.0001). OS was significantly longer in the erlotinib arm compared to the placebo arm in the overall population (12.0 vs 11.0 mos, HR=0.81, 95% CI:0.70-0.95, p=0.0088).[132] FDA approval for erlotinib in the maintenance setting was based on the results of the SATURN trial.[118]

Another trial evaluated the sequential administration of chemotherapy plus erlotinib vs chemotherapy plus placebo (switch maintenance) among 451 unselected patients. Wu *et al* published the results of the FASTACT2 trial, conducted in China, in 2013.[133]. The primary endpoint was PFS and other endpoints included RR and OS. Eligible patients were those diagnosed with stage IIIB/IV NSCLC, had a ECOG PS of 0-1 and had measurable disease. Excluded patients included those with brain metastases, spinal cord compression, or HIV, those previously treated with agents targeting the HER axis, and those with recent surgery or radiation therapy.[133]

Patients were randomized in a 1:1 fashion to receive cisplatin or carboplatin plus gemcitabine followed by erlotinib or placebo (n=226 and n=225, respectively). In the overall population, RR was better in the erlotinib group compared to the placebo group (44% vs 16%, p<0.0001). Median PFS was longer in the erlotinib group compared to the placebo group, as was OS (7.6 vs 6.0 mos, HR=0.57, 95% CI: 0.47-0.69, p<0.0001 and 18.3 vs 15.2 mos, HR=0.79, 95%CI: 0.64-0.99, p=0.04200).

In the *EGFR*-positive population, increases in both response and survival endpoints were observed. In this population, 84% of patients in the erlotinib group achieved response compared to only 15% in the placebo group (p<0.0001). Median PFS and OS were also significantly improved for erlotinib group compared to placebo group (16.8 vs 6.9, HR=0.25, 95% CI: 0.16-0.39, p<0.0001 and 31.4 vs 20.6 mos, HR=0.48, 95% CI: p=0.0092).[133]

Epidemiologic Studies of Erlotinib

Several epidemiologic studies, described previously, that assessed *EGFR* testing in NSCLC patients also evaluated erlotinib utilization.[112-114] In the Shen *et al* study,

EGFR testing was significantly associated with erlotinib use. Approximately 5% of patients received erlotinib treatment.[113]

Enewold and Thomas reported that 6.3% of all NSCLC patients received erlotinib in their study. Of patients with an *EGFR* mutation, 33.6% of all patients and 48.3% of stage IV patients received erlotinib. Erlotinib was less likely to be prescribed to in smokers (OR=0.27, 95% CI: 0.12-0.59) and patients with non-adenocarcinoma histologies (OR=0.14, 95% CI: 0.04-0.54). Erlotinib was not associated with increased survival.[112]

Approximately half (56%, n=36) of patients whose tumors were *EGFR*-positive received erlotinib in a study of Veterans.[114] Erlotinib was also prescribed to patients that were *EGFR*-negative (10%), had non-sensitizing *EGFR* mutations (11%), or whose *EGFR* status was unknown (17%). Erlotinib utilization was in agreement with the *EGFR* test results in 87% of the cohort cases. Patients who had an EGFR mutation and were treated with erlotinib had the best survival outcome (median=921 days, range=56-3730 days).[114]

Tables and Figures

Table 2.1. Selected FDA Approved Systemic, Targeted and Immune Therapies for Non-Small Cell Lung Cancer

Patient Population	First Line	Second Line and beyond
No *EGFR* mutation	Carboplatin/pemextrexed/pembrolizumab	Nivolumab
	Pembrolizumab*	Docetaxel
	Carboplatin/pemextrexed/bevacizumab	Ramucirumab/docetaxel
	Carboplatin/paclitaxel/bevacizumab	Pembrolizumab**
	Carboplatin/pemextrexed	Atezolizumab
	Carboplatin/paclitaxel	Pemetrexed
	Carboplatin/gemcitabine	Gemcitabine
	Carboplatin/docetaxel	
EGFR mutation	Afatinib	Nivolumab
	Erlotinib	Pembrolizumab**
	Gefinitib	Ramucirumab/docetaxel
	Osimertinib	Docetaxel
		Osimertinib
		Atezolizumab
		Pemetrexed
		Gemcitabine

Abbreviations: FDA, Food and Drug Administration
*For use in patients with high (≥50%) PD-L1.
**For use in patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR)

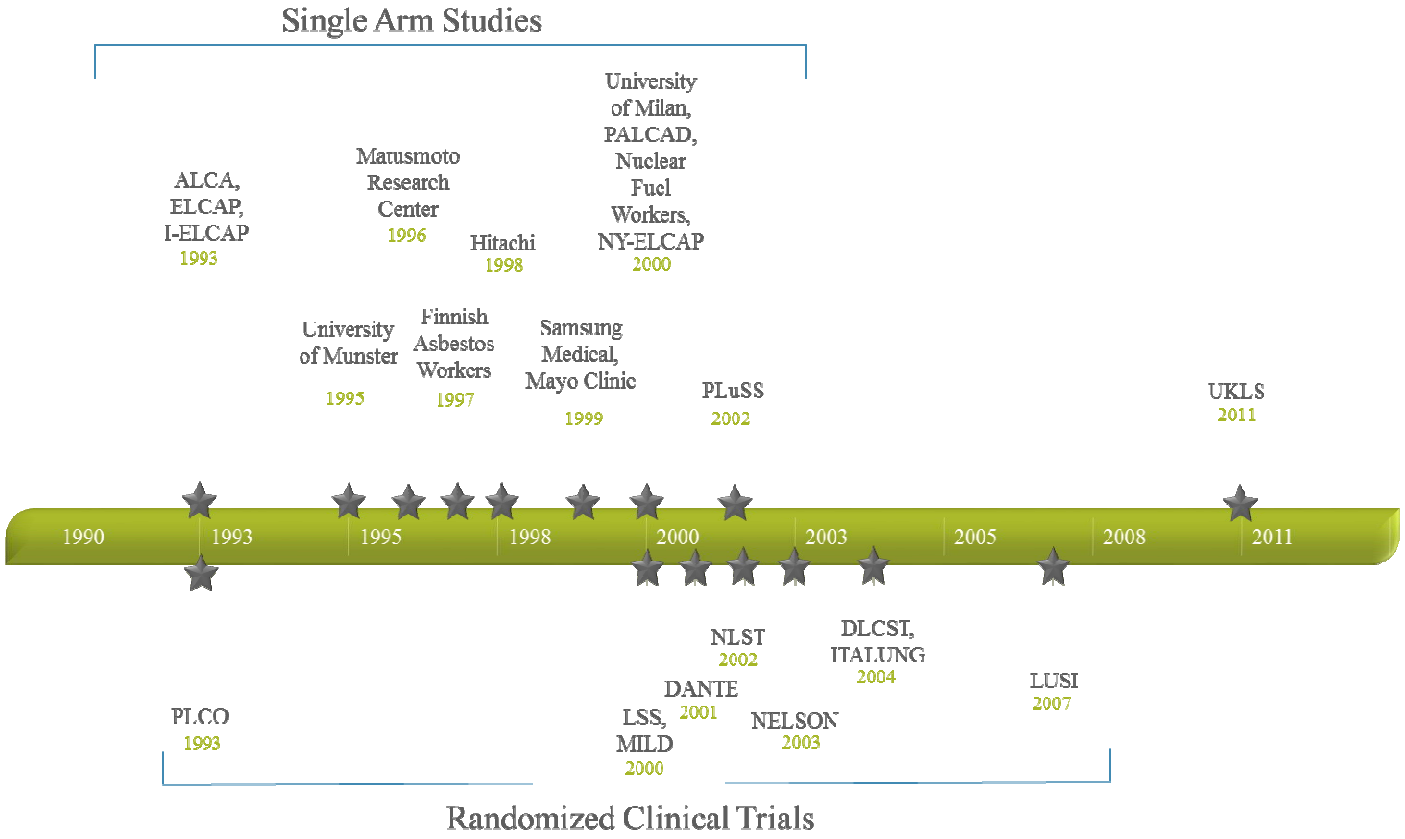
Table 2.2. Randomized, phase 3 clinical studies of erlotinib

Author / Study / Year	Country	Arms	Therapy	Patient Population / EGFR Testing Method	N	RR (%)	Median PFS (months)	Median OS (months)
Garassino *et al* TAILOR 2013	Italy	Erlotinib vs chemo	Second	*EGFR* wild type only SEQ	222	3.0 vs 15.5*	2.4 vs 2.9	5.4 vs 8.2*
Wu *et al* FAST-ACT-2 2013	Asia	Chemo plus erlotinib vs chemo plus placebo (sequential)	Switch maintenance	UNS SEQ	451	UNS: 43.0 vs 18.0* *EGFR*+: 84.0 vs 15.0*	UNS: 7.6 vs 6.0* *EGFR*+: 16.8 vs 6.9*	UNS: 18.3 vs 15.2 *EGFR*+: 31.4 vs 20.6
Karampeazis *et al* HORG 2013	Greece	Erlotinib vs chemo	Second and beyond	UNS SEQ	357	UNS: 9 vs 11.4 Erlotinib/ *EGFR*+ vs *EGFR* wild: 33.3 vs 7.3*	UNS: 3.6 vs 2.9 Erlotinib/ *EGFR*+ vs *EGFR* wild: NA	UNS: 8.2 vs 10.1 Erlotinib/ *EGFR*+ vs *EGFR* wild: 23.0 vs 9.7
Ciuleanu *et al*	INT	Erlotinib monotherapy	Second	UNS	424	7.9 vs 6.3	6.3 vs 8.6 weeks	5.3 vs 5.5

TITAN 2012		vs chemo		IHC and SEQ		*EGFR*+ IHC: NR *EGFR*+ SEQ: NI	*EGFR*+ IHC: NR *EGFR*+ SEQ: NI	*EGFR*+ IHC: 5.6 vs 5.5 *EGFR*+ SEQ: NI
Rosell *et al* EURTAC 2012	France, Italy, Spain	Erlotinib monotherapy vs chemo	First	*EGFR* mutation positive only SEQ	174	64.0 vs 18.0*	9.7 vs 5.2*	19.3 vs 19.5
Lee *et al* TOPICAL 2012	UK	Erlotinib vs placebo	First	UNS SEQ	670	UNS: 4.3 vs 2.2 *EGFR*+ sequencing: NA	UNS: 2.8 vs 2.6 *EGFR*+ sequencing: 4.8 vs 2.9	UNS: 3.7 vs 3.6 *EGFR*+ sequencing: 10.4 vs 3.7
Zhou *et al* OPTIMAL 2011	China	Erlotinib vs chemo	First	*EGFR*-mutated only SEQ	165	*EGFR*+ SEQ: 83.0 vs 36.0*	*EGFR*+ SEQ: 13.1 vs 4.6*	*EGFR*+ SEQ: NR
Cappuzzo *et al* SATURN	INT	Erlotinib vs placebo	Switch maintenance	UNS IHC and SEQ	884	UNS: 11.9 vs 5.4* *EGFR*+	UNS: 12.3 vs 11.1* *EGFR*+	UNS: 12.0 vs 11.0* *EGFR*+

2010						IHC: NA EGFR+ SEQ: NA	IHC: 12.3 vs 11.1* EGFR+ SEQ: NA	IHC: NR *EGFR*+ SEQ: NR
Gatzemeier *et al* TALENT 2007	INT	Erlotinib plus chemo vs placebo plus chemo	First	UNS IHC	1,172	31.5 vs 29.9	7.9 vs 5.4*	43 vs 44.1 weeks
Herbst *et al* TRIBUTE 2005	US	Chemo + erlotinib vs chemo + placebo (concurrent) followed by maintenance erlotinib monotherapy	First	UNS IHC	1,059	21.5 vs 19.3	NA	10.6 vs 10.5
Shepherd *et al* **BR.21** **2005**	INT	Erlotinib vs placebo	Second and beyond	UNS IHC	731	8.9 vs <1.0*	2.2 vs 1.8*	6.7 vs 4.7*

Bold text indicates a study in which FDA approval was based.
*Indicates statistical significance of $p<0.05$.
Abbreviations: IHC, immunohistochemistry; INT, international; NA, not assessed; NI, not interpretable; NR, not reported; OS, overall survival; PFS, progression free survival; PS, performance status; RR, response rate; SEQ, sequencing (DNA); UNS, unselected; US, United States



Abbreviations: ALCA-Anti-Lung Cancer Association, DANTE-Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays, DLCST-Danish Lung Cancer Screening Trial, ELCAP-Early Lung Cancer Action Program, I-ELCAP-International Early Lung Cancer Program, ITALUNG-ITALUNG, LSS-Lung Screening Study, LUSI-Lung Cancer Screening Intervention, MILD-Multicentric Italian Lung Detection, NY-ELCAP-New York Early Lung Cancer Action Project ,PALCAD-ProActive Lung Cancer Detection, PLCO-Prostate, Lung, Colon, and Ovarian Cancer Screening Trial, PLuSS-Pittsburg Lung Screening Study, NELSON-Nederlands Leuvens Longkanker Screeningsonderzoek, NLST-National Lung Screening Trial, UKLS-United Kingdom Lung Screening

Figure 2.1. Timeline of Single Arm and Randomized Studies of Low-Dose Computed Tomography

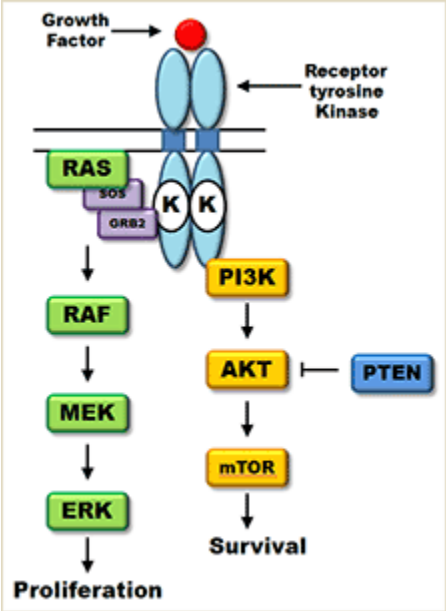


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Figure 2.2. *EGFR* Signaling Pathway

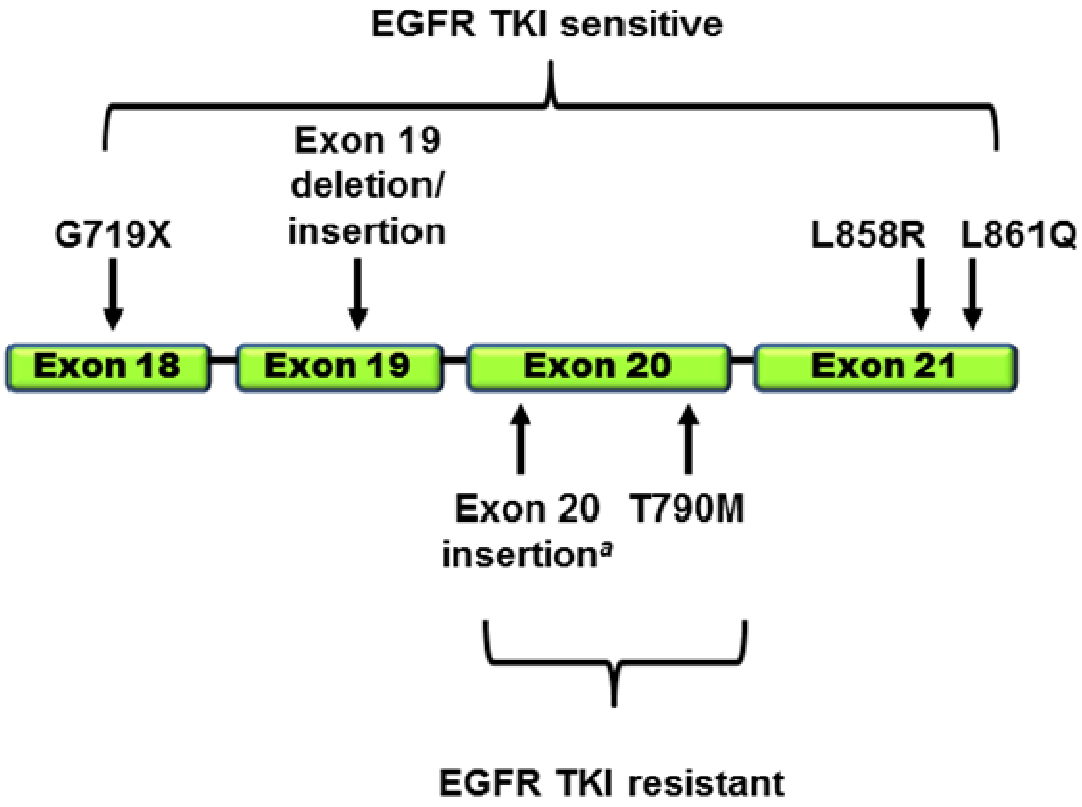

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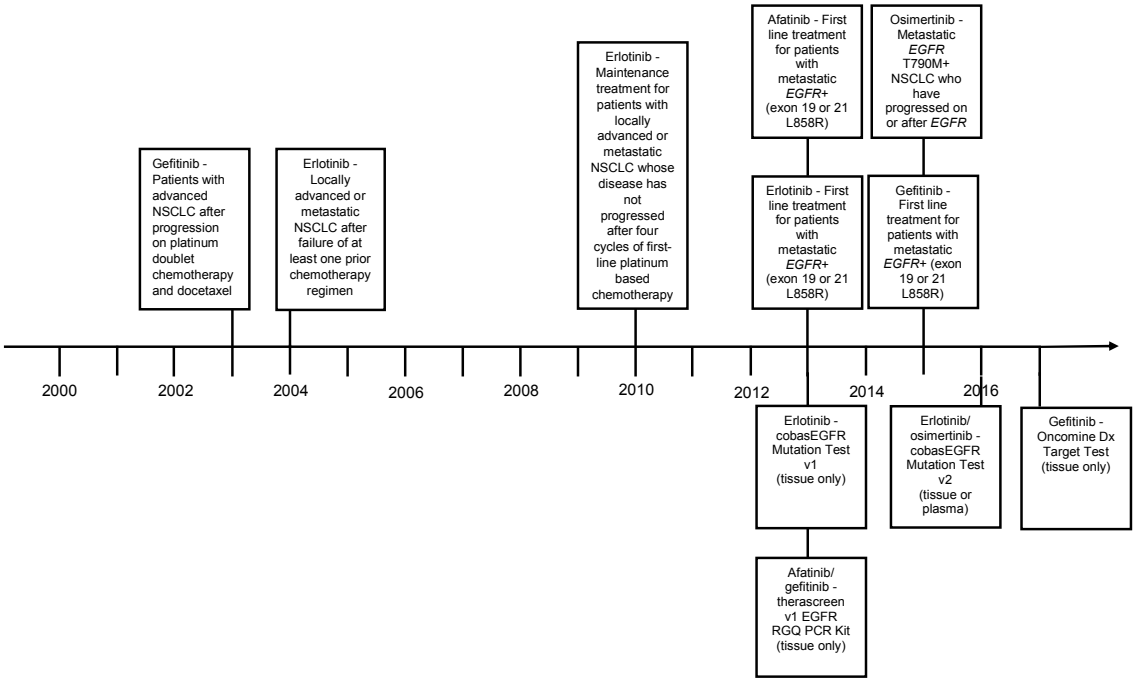
Figure 2.3. *EGFR* in Non-Small Cell Lung Cell



Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; PCR, polymerase chain reaction; RGQ, rotor-gene Q

Figure 2.4. Timeline of EGFR TKI and companion diagnostic approvals

CHAPTER III:

OBJECTIVES AND METHODS

Study 1: Family Physician Perceptions and Experiences with Low-Dose Computed Tomography Screening for Lung Cancer

Objectives

The main objective of this study was to quantitatively and qualitatively evaluate current family physician perceptions and experiences towards lung cancer screening with LDCT. Specifically, we assessed FPs' knowledge of the evidence supporting lung cancer screening and patient eligibility criteria. Additionally, we explored attitudes and experiences related to patient selection, shared decision-making visits, LDCT referrals, and LDCT follow-up practices.

Methodology

This sequential explanatory mixed-methods[134] research approach consisted of quantitative electronic questionnaire data followed by the collection of qualitative guided audio interview data. First, a quantitative questionnaire was administered to two primary care physician cohorts using Qualtrics software (Appendix A). In January 2015, members of the South Carolina chapter of the American Academy of Family Physicians (SCAFP) were sent an email containing a link to the survey (n=1,330). A follow-up email reminder was sent on January 22, 2015. The questionnaire consisted of a total of 32 questions (22 multiple-choice, 7 fill in the blank, 3 Likert scale) and took approximately

20 minutes to complete. A total of 85 SCAFP physicians started the electronic survey, with 65 completing the survey. To increase sample size, additional paper questionnaires were distributed to physicians attending the SCAFP Summer Breakaway and Annual Assembly (June 7-12, 2015). Paper questionnaires were placed in registration bags (n=135) and physicians were directed to submit the completed questionnaires at the University of South Carolina exhibitor booth. A total of 16 physicians completed the paper questionnaire (total sample size = 101). The last question in the questionnaire asked physicians if they agreed to be contacted for future research. A total of 19 physicians provided contact information. Additionally, primary care physician employees of the Carolinas HealthCare System (CHS) were surveyed. These physicians, located in North and South Carolina, were emailed a link to the survey in May 2015, several months after the CMS coverage announcement decision was made. A total of 57 physicians responded to the email survey. Results of this quantitative assessment were published in 2016.[16,17] Importantly, the results of the survey were used to develop the qualitative interview guide.

Qualitative data was obtained through convenience sampling to better and more deeply understand both urban and rural family physician perceptions towards and practices surrounding lung cancer screening. Participants in the qualitative phase of this study included a subset of those who participated in the quantitative survey. Additionally, we mailed personalized invitations to a sample of family physicians from North and South Carolina identified from the American Medical Association (AMA) Physician Masterfile. FPs were asked to return the invitation, using a provided RSVP card, to indicate their interest in participating. FPs were also recruited by referral from a

non-profit cancer advocacy group in North Carolina. The interviewer followed a semi-structured interview guide (Appendix A). Questions were developed based on responses to the survey, as well as Cabana's framework.[135]

Data Collection

The interviews took place until thematic saturation was reached and took approximately 30-40 minutes to complete. Due to the geographic spread of physicians in the SCAFP and CHS cohorts, the interviews were conducted via Skype and were limited to audio recordings only. No video recordings were made. Interviews were audio recorded using Call Recorder for Skype, transcribed verbatim, and reviewed for accuracy to ensure data quality.

Analysis Plan

Following quality review, the interview transcripts were assessed to develop a theme dictionary. Transcripts were then uploaded to NVivo qualitative data analysis software (QSR International Pty Ltd. Version 10, 2012) for thematic coding. Using a constant comparison technique, transcribed interviews were reviewed throughout data collection and the interview guide was adapted along the way to further explore relevant concepts identified during the initial interviews. The interview transcripts were then critically assessed to identify themes and subthemes by two separate persons. Any discrepancies in coding were discussed until consensus was met. Data was assigned to multiple themes.

Study 2: Molecular Testing Utilization and Targeted Therapy (Erlotinib) Administration and Survival Among Patients with Late Stage Non-Small Cell Lung Cancer

Objectives

The main objective of this study was to identify factors associated with receipt of molecular testing and erlotinib in patients diagnosed with late stage NSCLC residing in South Carolina. Additionally, we evaluated overall survival among molecular testing (yes/no) and erlotinib (yes/no) groups.

Methodology

This study involved the use of state-level data obtained from the South Carolina Central Cancer Registry (SCCCR) and the SC Revenue and Fiscal Affairs Office (RFA). The SCCCR is a population-based system that collects data on newly diagnosed cancer cases in South Carolina. Data in the SCCCR includes information on demographics, diagnosis date, cancer location and histology, treatment, and overall survival. The majority of information on cancer cases in the SCCCR is reported electronically from hospitals with existing cancer registries. However, some information is collected by SCCCR staff (i.e., independent pathology labs, free-standing treatment centers and physician offices, and non-registry hospitals). The quality of data from the SCCCR is good and undergoes quality control audits. The SCCCR has received Gold or Silver certification from the North American Association of Central Cancer Registries every year since 1997.

The SC Revenue and Fiscal Affairs Office (RFA) is an independent agency that houses administrative claims data from both the SC State Employee Health Plan

(SCSEHP) and SC Medicaid plan members. The RFA developed a series of algorithms using various combinations of personal identifiers to create its own unique identifier, enabling statistical staff to "link across" multiple providers and settings. Hence, it allows for linkages while protecting confidentiality of the client. The SC RFA and SC Central Cancer Registry frequently work together to complete data linkage requests for researchers in SC.

A cohort of patients from the SCCCR with a diagnosis of stage IIIB/IV non-small cell lung cancer from January 1, 2002 through December 31, 2012 was assembled. The cohort was linked to the same patients in the SCSEHP and Medicaid datasets. The resulting combined dataset was used to conduct all analyses.

In this project, we evaluated utilization of molecular testing and the EGFR TKI, erlotinib, using CPT codes and National Drug Codes (NDC), respectively, to identify patients who received molecular testing or erlotinib after diagnosis of lung cancer. CPT and NDC codes to be used in this analysis are listed in Appendix C. Additionally, we identified factors associated with molecular testing and erlotinib use. Lastly, we evaluated the impact of molecular testing and erlotinib on survival.

Analysis Plan

Descriptive statistics for patient and provider characteristics were summarized for the overall cohort and by 1) molecular testing status and 2) erlotinib status. Comparisons between molecular testing and erlotinib groups were performed using chi-square tests for categorical variables and a two-sample t-test for age. Univariable and multivariable logistic regression were used to identify factors that significantly predicted molecular

testing or erlotinib utilization. Odds ratios (OR) and corresponding 95% confidence intervals (CI) will be estimated. Covariates included in the final multivariable model will be determined using backwards elimination procedures.

Kaplan–Meier techniques will be used to estimate survival distributions and log-rank tests compared the survival distributions for the 1) molecular testing and 2) erlotinib groups. Univariable Cox proportional hazards regression was used to identify individual prognostic factors predictive of overall survival and multivariable Cox proportional hazards regression was used to evaluate the independent impact of the covariates and molecular testing status on overall survival. Unadjusted and adjusted hazard ratios (HR) and corresponding 95% CIs were estimated. Cox proportional hazards models were also estimated using propensity scores as covariates in parsimonious and non-parsimonious models.

All statistical analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS Inc., Cary, NC). All hypothesis testing was 2-sided with a $p<0.05$ level of statistical significance.

CHAPTER IV:

A QUALITATIVE STUDY OF NORTH AND SOUTH CAROLINA FAMILY PHYSICIANS' PERCEPTIONS AND EXPERIENCES WITH LOW-DOSE CT SCREENING FOR LUNG CANCER[1]

[1] Ersek JL, Turner G, Cartmell K, Sercy E, Adams SA, Hébert JR, Kim ES, Symanowski JT, Jan Eberth JM. To be submitted to Lung Cancer.

Abstract

Objectives: The United States Preventive Services Task Force recommends lung cancer screening (LCS) in high risk patients using low-dose computed tomography (LDCT). In 2015, the Centers for Medicare and Medicaid Services announced coverage of LCS shared decision-making counseling visits and LDCT. Despite this, LDCT utilization remains extremely low. This study assessed family physician (FP) knowledge of the evidence supporting LCS and patient eligibility criteria, as well as explore attitudes and experiences related to patient selection, shared decision-making visits, LDCT referrals, and LDCT follow-up.

Methods: We conducted a qualitative interview study using thematic content analysis. A convenience sample of 15 FPs in the Carolinas completed semi-structured Skype audio interviews. No information about LCS was provided prior to the interview. Interviews were transcribed verbatim and analyzed using NVivo software.

Results: Most FPs reported making a LDCT referral, however, the majority of FPs reported suboptimal awareness of the scientific evidence for LCS, patient eligibility criteria, and documentation and billing procedures. Smoking history was the primary driver of a FP's decision to discuss LCS. FPs were less likely to discuss LCS in patients with short life expectancies, comorbid conditions, or without insurance. While FPs knew they should limit discussions about LCS to high risk patients, they expressed willingness to screen outside of established criteria in certain circumstances. FPs preferred to conduct LCS discussions during annual visits, but acknowledged that many eligible patients do not visit the clinic unless there is an acute need. Barriers to LCS included

cost and administrative complexities, including lack of support resources and difficulties with documentation and billing.

Conclusions: FPs have varying degrees of knowledge about and experiences with LDCT. FPs are open to using LDCT as a LCS tool, with additional education and support.

Introduction

Despite advances in lung cancer treatment, lung cancer remains a major cause of cancer-related death in the United States, due in part to the fact that the majority of patients are diagnosed with advanced disease. Early lung cancer screening approaches (e.g., sputum cytology, chest x-ray) were largely unsuccessful and no improvement in lung cancer mortality was reported. In 2011, the National Lung Screening Trial (NLST) concluded that annual screening for lung cancer using low-dose computed tomography (LDCT) resulted in a 20% reduction in lung cancer mortality and a 6.7% reduction in overall mortality compared to chest x-ray.[18] Subsequently, the United States Preventive Services Task Force (USPSTF) published an updated guideline recommending annual LDCT screening in high risk patients at the Grade B evidence level in December 2013.[19] As a result, high risk patients with private insurance were allowed the option to have LDCT screening at no cost under the Affordable Care Act. High risk was defined as a patient aged 55 to 80 years who had at least a 30 pack-year smoking history, who currently smokes or has quit smoking within the past 15 years. Shortly thereafter, in February 2015, the Centers for Medicare and Medicaid Services (CMS) released a decision memo announcing coverage of LDCT screening for high risk adults. CMS defines high risk individuals similarly to USPSTF criteria; however, the age range was reduced to a maximum age of 77 years and CMS notes that patients should be

asymptomatic. CMS requires documentation of smoking history and a counseling visit with the use of decision aids to review the risks and benefits of lung cancer screening (i.e., a shared decision-making visit; SDM). The SDM counseling visit should include discussions of the importance of annual screening, patient comorbidities, and patient willingness to undergo further evaluation and treatment if a suspicious lung nodule is identified, as well as undertake smoking cessation.[13] Thus, specific patient eligibility criteria must be met and documented for Medicare reimbursement. Professional organizations, in general, describe the implementation of SDM visit, smoking cessation counseling, and promote standardized follow-up for abnormal LDCT results as components of successful lung cancer screening programs.[13,19,136]

While LDCT screening in now approved in high risk patients, current research indicates that uptake of lung cancer screening guideline adoption has been slow in the primary care setting. A recent study by Jemal *et al* reported low rates (<4%) of self-reported LDCT utilization from 2010-2015.[84] Several quantitative studies have assessed family physician's knowledge and attitudes following USPSTF recommendations and CMS coverage announcements.[16,80-82] However, only one qualitative study, to our knowledge, has assessed family physician (FP) knowledge, attitudes, and practices since the CMS decision memo announcement that FPs could obtain Medicare reimbursement for LCS counseling visits.[14] To enhance the existing literature, we conducted a qualitative study to assess North and South Carolina FPs' knowledge of the evidence supporting LCS and patient eligibility criteria. Additionally, we explored attitudes and experiences related to patient selection, SDM visits, LDCT referrals, and LDCT follow-up practices.

Methods

A qualitative interview study was conducted using thematic content analysis. We selected this approach because of the highly structured nature of the research questions we had, which were broad. We wanted to capture a holistic understanding of LCS in the Carolinas, from physicians' knowledge-base of lung cancer screening to following up with patients after LDCT screening was performed.

A convenience sample of physicians were asked to participate in a 30-45-minute telephone interview between March 2016 and August 2017. Physicians were recruited via multiple methods including postal mail, email, and telephone. First, physicians that provided contact information upon completion of a questionnaire on LCS that we administered in 2015[16,17] were contacted via email and/or phone and invited to participate in this follow-up study. Additionally, we mailed personalized invitations to a sample of FPs from North and South Carolina identified from the American Medical Association (AMA) Physician Masterfile. FPs were asked to return the invitation, using a provided RSVP card, to indicate their interest in participating. FPs were also recruited by referral from a non-profit cancer advocacy group in North Carolina. The sample size goal was 12 interviews, based on the recommendation of Guest, Bruce, and Johnson,[137] however, we continued recruitment until we felt that thematic saturation was achieved. All physicians gave verbal consent to participate as part of the audio recorded interview. The University of South Carolina Institutional Review Board approved the study.

Data Collection

One interviewer (JLE) conducted all the FP interviews using a semi-structured interview guide. Topics addressed in the interview guide included current evidence and

guidelines for lung cancer screening, who to approach for lung cancer screening discussions, how the conversation about lung cancer screening was performed, making a referral for screening, and following up after a LDCT. The interview guide was developed in an iterative fashion, with input from epidemiologists, medical oncologists, and nurses. Prior to finalization, the guide was tested with a FP and lung cancer screening thought leader. We did not provide any structured education to FPs prior to the interviews. Additionally, we emailed participating FPs educational materials published by the Agency for Healthcare Research and Quality (ARHQ) upon completion of the interview.

Interviews were executed via Skype with the Call Recorder for Skype [Ecamm, North Andover, MA].[138] All interviews were recorded in their entirety and transcribed verbatim by individuals trained in dictation. Transcribed interviews were then reviewed for quality by the interviewer (JLE) and revisions to the transcribed interviews were made if required. Quality-checked interviews were then imported into NVivo® Qualitative Data Analysis Software version 11.4.[139] While interviews were reviewed for quality, an initial codebook was drafted (JLE) using a directed approach to content analysis.[140,141] The codebook was continuously reviewed and revised using the constant comparison technique[142] with input from two reviewers (JLE, GT).

Data Analysis and Interpretation

Reviewers independently coded each interview using NVivo® and codes documented by each reviewer were compared. A Cohen's Kappa coefficient was calculated for each node for each interview. An overall interview Kappa was calculated by averaging the Kappa values obtained for each node. The interview Kappa was used to

measure inter-rater reliability while accounting for the amount of agreement that could result by chance.[143] Interviews with overall Kappa coefficients approximately ≤ 0.75 (or excellent agreement)[144] were further compared and discussed among the reviewers until consensus was reached. We then queried the NVivo® database to build a report for each individual code and reviewed all the content within that code. Codes were refined and combined to identify key themes. A key theme was defined as a theme that occurred in the majority of FP interviews. The coding reports were then reviewed a final time and representative quotes were selected.

Results

Interviews ranged from 27-52 minutes. Overall interview kappa statistics ranged from 0.75-0.88. A total of 15 physicians completed the interview (NC=7, SC=8).

Physician and practice characteristics

Table 4.1 reports physician characteristics. About half were male. Almost all were non-Hispanic White and were at least 40 years old. Most were in a group practice. FPs practicing in 12 different counties in North or South Carolina participated.

About half of the FPs worked in clinics with at least 5 other employees and most worked full-time. There was a mixture of rural and urban clinics, as well as a mixture of hospital-based, academic, and community-based single or group practices. All but two FPs reported accepting Medicare/Medicaid patients and most saw a high proportion of these patients. The two FPs that did not accept Medicare/Medicaid worked at free clinics and submitted no claims for billing. A few FPs described having LCS programs in place at their practices.

All FPs saw middle age and senior patients and the majority described seeing patients with a "grab bag" of chronic diseases (e.g., heart disease, chronic obstructive pulmonary disease, diabetes, hypertension, arthritis, pain). FPs mentioned that in patients with comorbidities, the focus was compliance with therapies for their chronic disease and less importance was placed on preventive services and screening. Additionally, a few FPs described other cancer screenings as taking priority. All FPs described having patients with either active or remissive lung cancer and the majority reported seeing many smokers or heavy smokers.

Evidence and guideline knowledge

Table 4.2 includes a list of key themes and supporting quotes from participating FPs. The majority of FPs interviewed had *suboptimal awareness of the scientific evidence for LDCT screening*. Most physicians were aware of some of the evidence in support of LDCT screening (including the NLST and/or the PLCO studies), but few could recite specific details. A few were completely unaware of the scientific evidence supporting LDCT screening in high risk patients. Most physicians were able list at least some the organizations that supported LDCT screening, but a couple noted that these organizations have made "mistakes" or have changed their recommendations in the past. A few FPs reported inaccuracies about gender, stating that reductions in mortality observed from LCS in the scientific literature were not applicable in women.

Most FPs also had *suboptimal awareness of patient eligibility criteria for LDCT screening*. The majority of physicians incorrectly recited at least one of the main criteria (e.g., age, smoking pack-years, or current/quit smoking status). Only a few physicians reported not knowing any of the criteria and described looking up the criteria at the point

of care. A few FPs reported screening patients with symptoms (e.g., cough, weight loss), even though current recommendations pertain to asymptomatic patients.

Deciding on which patients to discuss lung cancer screening

A patient's *smoking history (e.g., length of time, volume smoked) was cited as the primary driver of a FP's decision to counsel patients on LDCT screening*. Patient age also was frequently reported as a driver of whether counseling should be initiated. A few FPs discussed various other patient exposures (e.g., cotton dust, secondhand smoke, coal dust, asbestos, silicon dust) that would motivate them to initiate counseling, and a few described targeting individuals with known lung disease as candidates for screening, even though these patient groups are not listed in the current criteria defining high risk patients. A few FPs incorrectly reported that gender should also be considered and that screening "doesn't apply to women".

The majority of FPs felt that screening should be limited to those who fit the criteria for high risk, although there was sometimes uncertainty about the specific criteria. Some FPs reported not approaching patients with *short life expectancies or comorbid conditions*, in alignment with current recommendations. Some FPs also reported *choosing not to engage in counseling about LDCT screening with uninsured patients* due to concerns over the patient's ability to pay for the LDCT and follow-up diagnostics. Some FPs also described that it "wasn't fair" to discuss screening with a patient that would likely not be able to afford screening. Other FPs felt that counseling about LDCT should be done with all high risk patients, regardless of insurance status and that "judgements" about a patient's ability to pay for screening should not dictate the decision to initiate counseling.

Most FPs indicated that they *know that they should initiate discussion in high risk patients only*, but are willing to engage in counseling and make LDCT screening referrals for patients who do not fit the criteria for high risk if the patient requested screening or if "anything strikes them…that they should undergo screening", indicating that they felt other factors would influence their decision to initiate a screening discussion. Henderson et al reported that physicians were more likely to order screening when a patient requested it.[73] Importantly, when discussing lung cancer screening in lower-risk patients, FPs frequently described explaining to their patients that they may have out-of-pocket radiology costs and that "they [the patient] will have to see if their insurance would cover it". However, FPs reported that they felt most patients were not interested or "do not want to know [if they have lung cancer]" and *rarely initiated screening discussions themselves*. Of the few patients who do ask, FPs described patients to be former or current smokers, more education or health conscious or to have a family member recently diagnosed with cancer. A few providers stated that their patients asked for chest x-ray, not LDCT. Only a few FPs described dissuading lower risk patients from having screening and steering the conversation more towards smoking cessation.

Lung cancer screening discussion and low-dose CT referral

Most *FPs felt that the screening discussion and referral is their responsibility* because FPs knew the patient's values and social issues (e.g., transportation needs). When asked if pulmonologists could or should discuss lung cancer screening with patients, FPs felt that pulmonologists were certainly qualified to have these discussions. However, concern that not all patients would have access to a pulmonologist deters FPs from the idea of large scale implementation of lung cancer screening programs at

pulmonology clinics. Additionally, one FP expressed concern that pulmonologists and/or radiologists may not truly be able to give an unbiased explanation of the pros and cons of lung cancer screening because they stand to profit from low-dose CTs. While most physicians *felt comfortable conducting shared decision-making (SDM) counseling visits* with their patients, some FPs reported the need for additional education on the risks and benefits of lung cancer screening to truly implement SDM properly. One FP stated, "I would be comfortable. I probably need to review the specifics of the risks and benefits of the procedure first, but yeah, I would be comfortable doing it." Many described scenarios where they present screening pros and cons and then let the patient make the decision. One FP described SDM as an "arm twist" where he explains to the patient that he "doesn't have to do this" and states that usually patients will agree to it if you're recommending it. Only a couple of FPs reported that they took a more paternalistic approach. One felt that the decision to engage in SDM or paternalism is really patient-driven. The FP said, "I guess the way I described it sounds more like benign paternalism, or benevolent paternalism…but umm, I do try to engage my patients in that shared decision-making, and then the ones who I feel like would be willing to cooperate, I will bring things out…tell me what your values are, and…I'll tell you the kind of things I recommend. I try to bring that stuff out, but it doesn't really work for everybody. So, I can't say that I always take that approach." No FPs mentioned the use of decision aids as a tool to conducting SDM.

Most FPs *prefer to conduct lung cancer screening discussions during annual or wellness visits*. While this was the preferred setting, some FPs were concerned that the patients most appropriate for screening were more likely to be seen in the clinic only for

acute health issues and often missed annual wellness visits. One FP stated, "I can't really get them to come to the office dependably once a year…usually [they schedule a visit] for some acute need and we just wouldn't get around to that [lung cancer screening]." Most FPs reported challenges to conducting SDM during acute or sick visits and stated that they were less likely to have adequate time (if any). Some of these challenges included addressing other health concerns (i.e. ongoing chronic conditions, such as hypertension and diabetes, or acute needs, such as flu or infections) or the need to discuss "higher priority" cancer screenings (e.g. breast, cervical, or colon).

Most providers felt they could *adequately conduct shared decision-making for lung cancer screening in 10 minutes or less* during planned annual or wellness visits, however, some FPs reported the length of the discussion is dependent on the patient's questions and whether they were on schedule that day. One FP stated that they would consider initiating SDM "...if I'm not behind…" but quickly added "I'm so frequently not ahead". Scheduling the patient for a separate visit was an option discussed by FPs when time is limited, but FPs stated multiple reasons as to why they would prefer not to make a follow-up appointment solely for lung cancer screening purposes. These included additional cost of patient co-pays and patient compliance. One FP simply said that "it's hard for me to make appointments for just that [lung cancer screening]" and explained that the patient was unlikely to show up.

FPs reported that *education on smoking cessation is a key component to counseling patients on LDCT screening*. Some FPs also described conversations where they presented the patients with details on the risks and benefits of screening. Several FPs specifically mentioned telling their patients that a risk of screening is increased radiation

exposure. Less emphasis was placed on educating patients on the need to complete screening annually, with only a few FPs mentioning this topic.

Overall, FPs agreed that counseling for LDCT screening was feasible in their clinic, but that adjustments and processes to do this type of visit had either already been implemented or needed to establish. *Many FPs reported making at least one referral for LDCT screening*, however, a couple FPs confused screening with diagnostic testing and upon additional questioning, it was determined that they really made a diagnostic CT referral for a symptomatic patient. Only one physician reported making no LDCT referrals. Most FPs reported no major challenges making the referral, even in clinics without organized lung cancer screening programs. A few FPs described *having minor challenges (e.g., radiologists had a question or there was pushback from the billing processor) before a lung cancer screening program was implemented in their practice*.

Low-dose CT follow-up

The majority of FPs described *feeling responsible for informing their patients of their LDCT screening results*, however, some agreed that pulmonologists or radiologists could conduct SDM adequately. One FP had an opposing view and described one way to administer a lung cancer screening program would be through radiology clinics. She went on to describe how she could refer the patient to that department where, in the same day, the radiologist they could handle the SDM discussion, perform the LDCT scan, and give feedback on the results. She also suggested that the radiology clinic be responsible for following up with the patient if additional scans or procedures are needed. She basically felt that her role was to identify patients appropriate for screening.

Most FPs did not report any challenges in getting the result from LDCT scans. Many reported the scan being immediately available in their electronic medical record (EMR). Many FPs reported using phone calls to give good news or reports of "negative" scans and asking patients to come back to clinic to receive bad news about a "suspicious" finding. There were varying approaches to the management of suspicious findings. One FP reported making an immediate referral to a general oncologist and some FPs reported that their local oncologists would not see the patient until after an official diagnosis was made by tissue biopsy or bronchoscopy. One FP admitted not knowing what she was supposed to do regarding further follow-up and replied "I think I may have to beg ignorance. I'm not exactly sure what kind of result I'd get. Do I get something like a mammogram, where I'd see something suspicious on their CT and they'd need a biopsy next? I don't know enough about what the next step would be. If that would be a referral to a general surgeon or cardiothoracic, biopsy, bronchoscopy, I don't know."

Pulmonary nodule clinics could play a role in lung cancer screening, but FPs had varying levels of knowledge as to whether pulmonary clinics existed in their geographic area. Only a couple FPs reported with certainty that they had a pulmonary nodule clinic in their area dedicated to evaluating suspicious lung nodules. A couple of FPs described patients having to travel too far to receive that type of specialty care or not having access to specialty care at all.

Barrier and facilitators to implementing lung cancer screening in the clinic

Not surprisingly, a majority of FPs reported *cost (e.g., patient visit co-pay or radiology fee) as a barrier to LDCT screening*, even for insured patients. Most FPs reported that the cost was either unknown or was too high. Specifically, one FP said "So,

we don't know the prices, we don't know the costs, and many, many, many folks ask questions about what this is going to cost." For most FPs, there were no LDCT financial assistance programs in their area for asymptomatic patients, although some financial assistance programs were available for symptomatic patients to get diagnostic scans. While most FPs reported getting LDCTs paid for as a barrier, most FPs described no issues with getting a patient treated if a lung cancer was diagnosed. In fact, one FP stated "yeah, it's a done deal after the diagnosis is made, that's not even a problem." Emergency Medicaid and indigent care programs were reported as approaches for getting lung cancer treated in uninsured patients. One FP described "fabricating symptoms" to move a patient into the "diagnostic" category so that the scan would be covered or using different, more historical approaches, such as calcium scoring exams to get an image of the lungs. This particular FP thought ordering calcium score exams were a "2-for-1" approach to disease detection. He stated that this exam captured information most of the lungs (85%) as well as the heart. Using this approach, he felt, provided information on detecting both lung cancer and coronary artery disease, two diseases in which smoking is a risk factor.

Some FPs mentioned administrative barriers to LDCT screening that included *lack of support staff* to assist with preparation or execution of SDM counseling visit (e.g., nurses, other ancillary staff) and no established practice quality metrics requiring lung cancer screening to be performed (as is the case with other cancer screenings). A majority of FPs had *suboptimal knowledge on the complex documentation and billing procedures for LDCT screening*. Many either did not know that they could submit claims for a lung cancer screening counseling visit or did not understand all the documentation

requirements for a Medicare claim to be processed (e.g., LDCT written order with documentation of age and smoking history, evidence of SDM visit with use of a decision aid, and smoking cession counseling).

All FPs reported some type of *time constraint as a barrier* to lung cancer screening discussions. Some FPs reported time constraints that resulted from *overbooked schedules and reported often "running behind"* and others discussed time barriers in reference to *competing health issues being prioritized over lung cancer screening* during already short office visits. Of the entire group of FPs interviewed, only one FP felt so strongly about lung cancer screening that she reported "always" making time for it, despite her overloaded schedule and time constraints.

FPs had some ideas that would facilitate lung cancer screening discussions with their patients. Patient education (e.g., take-home materials, print and video media campaigns) and systematic approaches to identifying guideline appropriate patients in the clinic were suggested. EMR pop-up reminders, paper chart notifications, and patient completed screening tools (used in the waiting room) addressing multiple screening topics were systematic approaches described by FPs as facilitators. "…one of the answers would be a good EMR. What do they call them, kiosks? You know or patient check in module things? Well, yeah, it's interactive too…and keep going down menus based on their answers. Just like a human interview would do. So that will be helpful." Few providers mentioned patient financial assistance programs as potential facilitators.

Discussion

This qualitative assessment aimed to provide an in-depth look at family physician knowledge and perceptions towards LCS, as well as their experiences implementing (or

not implementing) screening in their practice. In comparison to other recently published qualitative studies on this topic,[14,15,78] we did not provide any structured education on lung cancer screening prior to our interviews, allowing us to gain insight into what practicing FPs may know and practice without any direct influence. While the FPs we interviewed described many challenges, the majority felt that LCS was feasible in their clinics, with some additional education, planning, and assistance.

FPs had suboptimal knowledge of the scientific evidence and patient eligibility criteria for LDCT screening, but welcomed education on these topics. Uncertainty about who is eligible for screening and the scientific evidence that underlies screening guidelines has been reported across both quantitative and qualitative research studies, rural and urban geographic areas, physicians and advanced care providers, and community-based, Veteran, and academic-based practices.[14,15,73,75,78,80,82,83] Raz *et al* reported that less than half (47%) of primary care physicians surveyed in Los Angeles county were aware of the USPSTF recommendations for lung cancer screening and many could not identify when LDCT was recommended and not recommended. Another survey study, conducted by Duong et al found that only 31% of PCP providers answered age and smoking criteria correctly.[83] Simmons *et al* conducted telephone focus groups with physicians, nurse practitioners, and physician assistant and reported that the majority of the providers had limited knowledge on LCS.[14] Despite limitations in knowledge, providers across studies were open to receiving additional education about lung cancer screening and incorporating it into their practice,[14,83] similar to the providers in our study. The FPs interviewed in this study also were uncertain about the requirements for documenting and submitting claims for reimbursement, an education gap not previously

highlighted. Interestingly, despite the CMS requirement that a shared decision-making counseling visit incorporated the use of a decision aid, not one FP we interviewed described using a decision aid in their LCS discussions. This lack of emphasis on the importance of using a decision aid is in contrast to a recent electronic survey study by Triplette *et al* where 51% of PCP and pulmonary providers reported decision aids as an important facilitator to LCS discussions.[82] When asked about billing for lung cancer in general, many physicians reported not being aware that they could bill for SDM counseling visits and/or LDCT.

We found that smoking history, one of the criteria for defining high risk patients, was the primary driver of a FP's decision to initiation LCS. Smoking history and secondhand smoke exposure were also reported as drivers of the decision to initiate lung cancer screening discussions by Henderson *et al* in 2011.[73] However, we also found that FPs were willing to screen patients outside the established criteria for a high risk patient if the patient was requesting screening or if the FP was motivated by factors not addressed in the recommendations, such as family history, secondhand smoke exposure, or occupational exposures. Henderson (2011) described confliction over ordering LDCT in lower risk patients as something they coined the "physician struggle", meaning that FPs may make decisions about screening that are contrary to their beliefs about screening as they contemplate other factors, such as patient requests or presence of other risk factors. Propensity to screen patients outside of guidelines (over screening) has been reported previously,[73] is a concern across cancer screening programs, and results in increased financial burden at the population level. Other qualitative studies reported provider concerns over litigation resulting from failure to suggest screening prior to a

lung cancer being diagnosed;[73,78] however, this concern was not described in any of our FP interviews.

Some of the FPs in our study also reported using other approaches to get some form of screening for patients, such as use of other scanning modalities, or ordering diagnostic tests for truly asymptomatic patients. Prior research has documented continued use of CXR or other less preferred computed tomography scans,[14,15,73,78,81,82] however, the use of CXR was not commonly reported amongst our FPs. Hoffman *et al* reported in 2015 that no primary care providers had ordered a LDCT[78] and other studies have reported subpar rates of LDCT utilization.[74,75] More recently, Duong et al reported that 58% of providers surveyed reported ordering LDCT[83] and in our qualitative assessment, most FPs reported making at least one LDCT referral, perhaps suggesting a shift away from the use of CXR.

Several studies on LCS report financial concerns as a barrier to lung cancer screening.[14,75,78,80,81] Some FPs in our study also exhibited concern over discussing screening in underserved or uninsured patients, while some FPs felt that this was not a concern. This contradictory viewpoint appeared to be related to the availability of free or affordable screening for uninsured/underserved patients in their geographic area. FPs also expressed concern over difficulty discussing the patient's portion of the cost of screening, regardless of insurance coverage or type. With the variety of insurance plans available, FPs felt they could not provide accurate estimates of what the patient out-of-pocket cost for screening would be and must "speculate". A tool that could help providers determine the cost of a patient's copay would be useful and would promote more discussion. Another possible approach to addressing this barrier could be a phone

"hotline" for FPs to call for assistance. In addition to concerns about speculating on the cost of LDCT screening, FPs also had concerns about patient's out-of-pocket costs for follow-up diagnostics (e.g., biopsies, bronchoscopies).

Both quantitative and qualitative studies have reported that providers expressed the need for guidance (e.g., medical education)[78,83] and assistance advising patients about screening and follow-up care (e.g., point-of-care materials, additional staffing, multidisciplinary input).[15,78,82] A qualitative study by Kanodra *et al* described a LCS program administered in the Veteran's Administration (VA) in South Carolina, where primary care providers were notified of LCS eligibility via electronic medical record (EMR) notification and could then refer their patient to a nurse navigator who engaged in SDM with the patients.[15] VA providers viewed this LCS program structure as effective and efficient. While the FPs in our study largely felt comfortable conducting SDM counseling visits for LCS on their own, many reported time as a barrier and nurse navigator programs could potentially be an approach to handling time constraints. FPs had several other suggestions to facilitate LCS in their practices. EMR notifications were suggested by many FPs in this study as the best way to systematically identify patients, similar to other studies,[14,15] however they noted that the EMR must include a way to capture detailed information, including volume of cigarettes and length of time smoked (pack year history) and type of exposure (e.g., personal or second-hand), information that is less likely to be captured in existing EMR systems.

Several limitations should be considered when interpreting the results of this study. Our interview focused mainly on evidence and guideline knowledge, making decisions about who to approach for screening, and the LCS discussions. While we did

incorporate a broad range of topics, less emphasis was placed on documentation and billing for shared decision-making visits and LDCT follow-up. For example, we did not specifically ask about what FPs did when a patient had a borderline nodule and only one FP described his approach (referral to pulmonary for long term follow-up). Also, in our study, many FPs reported not knowing that they could bill for SDM counseling visits, limiting the questions we could ask about their billing processes. Lastly, our study interviewed only family physicians, leaving out an important population of individuals (e.g. nurses, advanced care practioners) that can participate in SDM visits and LDCT referrals in the primary care setting. These limitations highlight areas for further research. We had a diverse group of FPs from different geographic areas and practice settings and reached thematic saturation across our interviews, despite our smaller sample size.

Conclusions

Even though LCS with LDCT is a recommended cancer screening that is now covered by most private insurers and Medicare, FPs still have varying degrees of knowledge and experiences with LCS counseling visits, and while LDCT referral seem to be increasing, LDCT remains underutilized. This study suggests that FPs are open to using LDCT as an early diagnosis tool and consider SDM feasible in their clinics. If given appropriate education and tools, they would be more likely to utilize low-dose computed tomography for lung cancer screening.

Tables and Figures

Table 4.1. Descriptive characteristics of family physician participants by recruitment cohort

	SC AFP	CHS	AMA	Referral	Total
Gender					
Female	3	1	3	0	7
Male	5	1	1	1	8
Race / ethnicity					
Non-Hispanic White	7	2	4	1	14
Non-Hispanic Black	1	0	0	0	1
Age range					
20-29	1	0	0	0	1
30-39	1	0	0	0	1
40-49	2	2	3	0	7
50-59	1	0	0	1	2
60-69	3	1	0	0	4
State					
NC	0	2	4	1	7
SC	8	0	0	0	8
Practice Setting					
Group practice	3	2	4	1	10
Private practice	1	0	0	0	1
Hospital	1	0	0	0	1
Academic	2	0	0	0	2
Other	1	0	0	0	1
Specialty					
Family medicine	8	1	4	1	14
Internal medicine	0	1	0	0	1

Abbreviations: AMA, American Medical Association; CHS, Carolinas HealthCare System; NC, North Carolina; SC, South Carolina; SC AFP, South Carolina Academy of Family Physicians

Table 4.2. Key themes and supporting quotes

Topic	Key Theme(s)	Supporting Quote	Supporting Quote
Evidence and guideline knowledge	Suboptimal awareness of scientific evidence	*"I'm aware that there is research and that it is favorable, but I don't know the details, and it's because I haven't really been able to apply it very well at my current practice."*	*"I don't know about the scientific evidence behind it."*
	Suboptimal awareness of patient eligibility criteria	*"Umm, as far as who to screen, that's what I'm not as confident about. I know that older people and people who have a long smoking history, umm, would be certainly would be greater candidates than younger people or people who didn't smoke, but I don't know exactly what the age is or how much, how many cigarettes or any of that. That's the part that I would have to look it up."*	*"I'll have to be honest, as far as the specific patients or past history or patient age, I don't. I am aware that CT exists as an option but as far as recommendations as to who should have that, I don't really know. "*
Making the decision to discuss LCS	Smoking history is the primary driver of FP decision to initiate lung cancer screening counseling visit	*"Yeah, when they come in to the clinic, they fill out a, uh, intake form that that describes smoking history and so based on that form, we'd, you can sometimes, you can make the decision at that point if they need to have screening..."*	*"So I, yeah so all, all my smokers get a talking to..."*
	FPs are less to likely to discuss lung cancer screening in patients with short life expectancies and/or comorbid conditions	*"Well, [I wouldn't bring up screening in] people that are sick from other things, perhaps. Um, you know that you don't anticipate them getting benefits based on how ill they already are."*	*"...unlikely to survive long enough to benefit from, uh, having lung cancer diagnosed and an intervention."*

	FPs are less to likely to discuss lung cancer screening in uninsured patients	*"Hmmm, that's a tough situation. Uh…I don't even know that I would even bring it up for fear that it's going to be unaffordable. They're going to feel like they don't get wat everybody else gets because they don't have insurance. I don't think I would probably mention it."*	*"I don't think we have any programs in this community that pays for that. We have free mammograms but we don't' have any free stuff like that, so I'm not sure if I would mention it. It almost seems kind of cruel to mention it and know that they have no means to get it, but saying maybe when you're able or you know if your insurance goes through then and most people will get Medicare when they are 65, so if they're still appropriate then, then they can revisit it. So, I may or may not discuss it, sorry."*
	PCPs are aware that they should focus lung cancer screening discussions to high risk patient	*"…wouldn't recommend anything outside the guidelines."*	*"…you have to be the right age, 30 pack year history, not be a 15-year non-smoker, and willing to follow through with, if they have positive screenings, willing to follow through and willing to sustain and survive surgical recommendations if they have them. It's a very narrow population."*

Patient driven LCS requests	Patients rarely initiate lung cancer screening discussions	*"I think that there's, they know lung cancer is always there in the background, and umm they don't ask for screens because they don't want to know. That, that's kind of my feeling based on my patients. You know they're not, they're not asking, and even the ones that are savvy and have heard of it, uh they're not. Mentally, they don't want to know. I mean, they know every time they smoke, you know."*	*"It's rare, to be honest, but most of the ones that ask are usually moderate risk smokers tell me someone in their family was just diagnosed with lung cancer."*
	Physicians are willing to refer out of guideline patients for screening if a patient requests screening	*"So I mean if someone [who was not at high risk for lung cancer] asked me for something specific I try to either explain why I think it's a good idea, or if I, or not a good idea and if they don't, if they still don't agree with me and they still want that thing, then we explore, you know, what the outcomes might be. You know, uh for instance, if you get a screening and you find something you weren't expecting maybe it wasn't along these lines and then they need to be worked up further, you know we talk about risk and benefits. But, if people, people really want the screening and they are willing to pay for it even if their insurance doesn't, I certainly would be fine with ordering it."*	*"I would approach that with education. I would let them know that testing that they read about in Newsweek is only known to be helpful in these folks. For whatever reason, they don't fall into that category and we don't know if this test would be helpful for you and it may be harmful…because what they're requesting is help. I've had some folks who insist on a screening test even though I don't recommend it. I handle that like I would with any informed consent. I tend to lean on the side of getting the test for them and informed consent that the risk benefits may be more towards the risk and we are obligated to follow up with results and eyes wide open going in."*

LCS discussion and LDCT referral	Providers feel that the screening discussion and referral is their responsibility	*"I mean, I see it like I do any other kind of screening. I think it's my responsibility. Umm, we screen for colorectal cancer and cervical cancer and breast cancer, so why should we not also be screening for lung cancer?"*	*"Yeah, I think we need to do it because we are the front line and most folks see us first and they have that great relationship and trust with us so I think we need to be doing it absolutely."*
	Annual/wellness visits are the best time to conduct lung cancer screening discussions	*"If it's an annual checkup, I feel obligated to make sure they are caught up on all of their screenings because they are coming in for that specific purpose, the way I look at it. If they are coming in for chronic disease management or an acute visit, then I still feel the responsibility to make sure that we have done the appropriate screening processing with them and if time allows we will try and do it, but if not we make sure before they leave they have a follow up appointment with me to get that done."*	*"Certainly, screening tests are a huge part of discussion when you have someone in for that wellness visit, annual checkup, when we are already going through mammograms, bone density testing, colonoscopy, other immunizations, adult immunizations up to date. Um to add in, 'this is your history, you're at risk of lung cancer maybe we should consider this CT test', I think it would feel natural. I would be willing, I guess that is my answer, willing to add that to the discussion."*
	Shared decision-making discussions can be completed in 10 minutes or less	*"Well, it depends on how many questions the patient has. I if, if they just say, "well, ok sure," then, I mean I think it could be a five-minute discussion, and, and they would know enough and we'd be done."*	*"Let's be honest, that's a good 5-10 minutes to really do what we're supposed to be doing."*
	Providers are comfortable with shared decision-	*"Yes, [I am comfortable with it]. I do it [shared decision-making] all the time. I tell the patients the risks and benefits of lung cancer screening, and it's*	*"I mean I would say that I'm moderately at least moderately comfortable with that. I mean, I'm*

	making approach to lung cancer screening discussions	*their decision, not mine."*	*accustomed to, umm like, the concept of 'shared decision-making,' and when I have sufficient time and when I feel like my patients are willing to engage me on it, then I do that already, and I have discussed umm you know the guidelines as far as what's recommended for lung cancer screenings."*
	Education on smoking cessation is a key component to lung cancer shared decision-making discussions	*"Nowadays our conversations typically go like, 'you're not on any inhalers, your lungs sound clear, I would certainly encourage you to quit while you're ahead before any damage has been done to your lungs'."*	*"It's supposed to be done in conjunction with the smoking cessation counseling as well."*
	Majority of primary care providers have made at least one referral for low-dose computed tomography	*"I am doing it. I do make those recommendations. Again, at the time of the office visit, with time being limited, do I do it as often as I should be? The answer is no but do I do it, yes... I'm not sure what it was, but something made me change my practice to where I do recommend more lung cancer screenings now than I did a year ago."*	*"Yes, I have, but it's umm I mean I could count the number of people who allow me to refer them on one, maybe two hands."*
	Challenges making referrals has resolved with time	*"I didn't start making the referrals until I knew that there was a program in place. The place that I've been referring them to get the low-dose CT is not the usual place I refer for other radiologist studies. So, it's kind of a special scenario. So, I guess some difficulty because it wasn't a facility I usually use. But almost everybody I attempted to schedule, the test has been performed."*	*" I would say that prior to three or four months ago, yes it was very difficult because we had to order the CT scans ourselves and there was no option available for low-dose CT for the purpose of lung cancer screening. Prior to the comprehensive cancer center*

			stepping in February or March it was really difficult to get the referral in Epic. Now it is much easier, we just type referral for a lung cancer screening and it will pop up and it is pretty nice."
LDCT follow-up	FPs believe it is their responsibility to inform patients of low-dose computed tomography results	*"Well…it, uh, us…me the primary doctor. That, we do that, the positive screening and then we talked to them about making a formal diagnosis."*	*" I like to be more hands on with our patients and the local gals who do the mammogram know that. I'm always going to beat them to the punch before they call them back. There's your answer, I would rather be the one to tell, you know share that with the patient. Walk them through it and make the plan."*
	No challenges obtaining scan results	*"No [problems], the, the reports are readily available on the computer."*	*"Mhmm, yeah [scans are in EMR] and a lot of times they'll [radiologists] call if something shows up."-Sum*
	Pulmonary nodule clinics could play a role in lung cancer screening discussions	*"We work pretty closely with the pulmonology clinic for our COPD patients and asthma patients and that kind of thing and I'm not aware of them ever recommending screening for high risk patients. So now that we talked about it I'm curious to know if they ever recommend it, and how we could complement each other in that way...I, I absolutely would consider that, um, but it would only cover a small part of the patients that would*	*"Um, usually if nodules that are kinda iffy, I refer to pulmonology and then they usually follow them for a couple of years and if they are stable, they just hand them back to me."*

		potentially be eligible I would think."	
Barriers and facilitators to implementing LCS in the clinic	Patients have financial concerns	*"We have a strict policy of $80 copay [for counseling visits] just to see me if you don't have insurance and then I can talk about them [the recommendations for screening]. I can make recommendations and I can even give referrals but often times those referrals will get denied or not even scheduled because their insurance data, especially if their clean [asymptomatic]. Now if you are symptomatic, I am able to make a couple of phone calls and get the copay waived but general screening, that is a very difficult thing to do."*	*"Specifically, you know, how well is this covered and what's the out-of-pocket costs associated with having the screening completed. Folks have, nowadays they can opt maybe to have higher co-pay or deductible insurances and sometimes the benefit is available but there are still associated costs out of pocket. So, we don't know the prices, we don't know the costs and many, many, many folks ask questions about what this is going to cost."*
	Lack of support staff and practice or quality metrics are a challenge	*"I mean, we have these elaborate electronic medical records but it still proves to be a challenge to keep track of all the little, um, quality parameters and I'm not aware of lung cancer screening being a quality parameter in our system."*	*"I just don't know how something like this [is doable], without having some kind of protocolized system where there is some other ancillary health person who can really do the documentation that Medicare requires."*

	Suboptimal knowledge regarding complex documentation and billing procedures	*"You know, for a long time, we were still waiting on those codes, so even if we did it, how would we even get it done, and again a heavily weighted Medicare practice."*	*"Uh, my colleagues who are trying to see two or three times as many patients as I do in a day, um, are just not going uh to generate the, the volume of documentation sufficient to satisfy these kinds of, uh, of audits and wind up, uh, frustrated with the amount of time that's, uh, generated in the audit, and the negative impression that their patients get if they realize that their doctor/patient visit was not covered and they're, uh, being, uh, charged that they [their doctor] didn't document this discussion and so forth...just a few of those kinds of, uh, frustrations dissuade a lot of physicians from doing the right thing."*
	Busy schedule often leads to "running behind"	*"I feel l maybe 25% of the time, if someone is coming in, feasibly I could do it, umm, because I mean the issue with that, if I get really far behind because I've had that conversation with one person, then I won't be able to have it with the next one."*	*"...if I'm not behind and umm the patient has fits the criteria and I haven't spoken with it before, then it certainly would be a chance to grab them. Umm, I would I'm so frequently not ahead that I don't frequently, don't want, to add those things to visits that uh umm are not, not screening type visits."*

	Patients have other competing health issues that are prioritized over lung cancer	*"I tend to prioritize, I do try and do it, but lung cancer screening really hasn't gotten to the top of my radar quite yet, whereas breast cancer, cervical cancer, colon cancer screening are kind of already part of my problem visits, meaning that I'll check and see if they are up to date and if they are not, then I will usually mention those."*	*"Make it streamlined for the very, very busy primary care providers in and you know under-resourced Medicare-heavy population because I'm very, even though I know who I should be talking to, I'm very challenged. Once I'm in a room with a patient and I've handled you know the five healthcare maintenance and the diabetes follow-up things and whatever, and then they hit me with three things they need you to do, I honestly don't have time to talk about it."*
	Patient education materials facilitate lung cancer screening discussions	*"I think also something that would help us would be just more patient education. You know I've had so many people ask about, like, shingles vaccine when they see the commercial and you know it's like oh yeah, that's a great idea you know, um, so but just public information helps them to help us remember...yeah I mean people watch TV, that's how a lot of stuff, messages and things like that, maybe some flyers or something in the office would be helpful, but yeah people, really notice the commercials."*	*"I get in the situation where I say you know this is what I recommend, but think about it for a minute, talk to your family about it. Let me know if you change your mind. I may ask you next time but I won't fuss at ya. That kind of patient...it might be kind of helpful to have a little bit of a brochure. I might just hand ya a little brochure or pamphlet to say here's a little bit more information, look at it and we'll talk next time."*

	Systematic approaches to patient identification facilitate lung cancer screening	*"This is a good place where electronic records and electronic checking systems could be helpful. We've played with some of those but never really found one that played well with our EMR. Those little kiosks that check-in and ask the basic screening questions and if they're positive they keep going down to the menu so they can do a full screening. They can do all the screening tests. What's your age range, pack year history? All of that. So... one of the answers would be a good EMR...patient check in module things...so that will be helpful."*	*"Um, actually kinda like a lot of the other triggers we've built in for other stuff now, just sorta build the guidelines in so it's easier to identify the patients um and that's probably the biggest thing, is just identifying the people that qualify and then just making a check, so saying has it been done or not, what interval and we decide to follow up from there."*

Abbreviations: CT, computed tomography; LCS, lung cancer screening; LDCT, low-dose computed tomography

CHAPTER V:

FACTORS PREDICTING MOLECULAR TESTING AND ITS IMPACT ON SURVIVAL IN PATIENTS WITH ADVANCED, NON-SMALL CELL LUNG CANCER: A RETROSPECTIVE, POPULATION-BASED ANALYSIS USING ADMINISTRATIVE CLAIMS[2]

[2] Ersek JL, Symanowski JS, Kim ES, Adams SA, Hébert JR, Eberth JM. Submitted to *Journal of Thoracic Oncology*, 11/17/17.

Abstract

Introduction: Lung cancer is the leading cause of cancer-related death in South Carolina (SC). Tumor molecular testing (MT) advances led to the development of precision medicine treatments, improving outcomes. However, disparities in MT utilization may exist. We evaluated factors related to MT utilization and the impact of MT on overall survival (OS).

Methods: Cases diagnosed with stage IIIB/IV non-small cell lung cancer (NSCLC) between January 1, 2002 and December 31, 2012 and available through the SC Central Cancer Registry were linked to SC State Employee Health Plan and Medicaid administrative claims data. Logistic regression (LR) was used to identify predictors of MT utilization. Kaplan-Meier methods were used to estimate survival distributions and log-rank tests compared the survival distributions between MT and no MT groups. Cox proportional hazards modeling was used to assess the impact of patient demographic and clinical characteristics (including MT) on survival, while adjusting for other prognostic covariates. Propensity scores were calculated and included as covariate in propensity-score adjusted Cox models.

Results: A total of 2,266 cases were eligible. In the multivariable LR model, predictors of having at least one procedure claim for MT included younger age (p=.008), in-state providers (p=.003), low tumor grade (p=.008), adenocarcinoma histology (p=.015), and diagnosis year of 2010 or later (p<.001). OS was longer in patients who received MT (median OS=13.0 vs. 6.0 months, p<.001). When adjusting for significant prognostic factors, patients with MT had a 43% lower risk of death compared to patients without MT (HR=0.57, 95% CI: 0.40-0.81, p=.002).

Conclusions: Several characteristics are associated with MT utilization. In patients with advanced NSCLC, MT may positively impact OS in the population-based setting.

Introduction

Lung cancer is the leading cause of cancer-related death in the United States and in South Carolina.[1,145] In 2017, approximately 4,320 new lung cancer cases and 2,920 lung cancer deaths are expected in South Carolina (SC) alone.[1] Over half of patients with lung cancer are diagnosed with advanced disease, contributing to the dismal 5-year survival rate of approximately 4%.[1] Historically, patients with advanced lung cancer have been treated with one of several platinum-based doublet chemotherapy regimens (e.g., cisplatin + paclitaxel or gemcitabine or docetaxel)or pemetrexed, none of which provided much hope for long-term response and improved survival.[4,146] Precision medicine, including targeted and immunotherapy drugs, may offer improvements in outcomes.

Within the last decade, advances in the genomic profiling of lung tumors have identified multiple alterations in lung tumor cells, especially non-small cell lung cancer (NSCLC), that can be targets for treatment. Various laboratory procedures are used to identify alterations in tumors including immunohistochemistry (IHC) to evaluate protein expression, *in situ* hybridization (ISH) to evaluate abnormalities in a specific region of nucleic acid on a chromosome, polymerase chain reaction to identify gene mutations, and sequencing to evaluate alterations in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).[147,148] For example, epidermal growth factor receptor (*EGFR*) is a cell surface receptor that can be evaluated using different laboratory approaches. *EGFR* is altered either by protein overexpression, increased gene copy number or genetic mutation.

EGFR is involved with cell proliferation, suppression of apoptosis, cell motility, invasion and angiogenesis.[20,25] Other targetable alterations found in lung tumors include *ALK*, *ROS1*, *BRAF*, and *MET*.[26,27]

Genomic, or molecular testing, has led to progress in treating advanced, NSCLCs and has allowed oncologists to use targeted approaches to treating selected patients, sparing many the systemic effects of cytotoxic therapies. However, little is known about the factors influencing molecular testing utilization in population-based settings. The purpose of this study was two-fold. We determined factors associated with molecular testing utilization among patients with advanced stage, NSCLC residing in SC. We also assessed the impact of molecular testing on overall survival.

Methods

Study Design, Data Source, and Cohort Selection

We conducted a retrospective cohort study using data from the South Carolina Central Cancer Registry (SCCCR) linked to administrative claims data obtained from the South Carolina Revenue and Fiscal Affairs (RFA) office. Eligible patients were those diagnosed with first primary stage IIIB/IV lung cancer between January 1, 2002 and December 31, 2012 who enrolled in the SC State Employee Health Plan (SCSEHP) or SC Medicaid during the study period. Patients with secondary malignancies and those insured concurrently by an HMO plan or who had Medicare as the primary payer were excluded.

Outcomes

Two outcomes were examined among patients in this study: 1) use of any molecular test, and 2) overall survival time in months. Prior to 2013, molecular tests were

coded using a billing method called "code stacking".[147,149] This method utilized a combination of Common Procedure Terminology (CPT) codes, consisting of laboratory procedure codes and reporting codes, to bill for molecular tests. Thus, different facilities could code for the same test in multiple combinations of stacked codes. In this study, patients with at least one procedure claim submitted with a CPT code indicative of molecular testing, codes 83890-83914, were categorized as having any molecular test ("yes") and patients without any claims utilizing codes were categorized as not having any molecular test ("no").

Overall survival was measured from date of first primary cancer diagnosis to date of death from any cause. Surviving patients were censored at the date of last SCCCR follow-up or December 31, 2014.

Covariates

Patient demographics

Age at diagnosis was evaluated as both continuous and categorical variables (<52, 52-57, 58-62, 63+ years). Race was categorized as White, Black, Other and Hispanic ethnicity as Hispanic, non-Hispanic, or unknown. Marital status was categorized as married, not married, or unknown. Insurance status was categorized as SCSEHP or Medicaid. Of note, all patients in this study had some form of insurance coverage, but did not have Medicare. Patient metropolitan status was derived using rural-urban continuum codes assigned to each patient's county of residence at diagnosis and were ultimately dichotomized as non-metropolitan (including rural) versus metropolitan counties.

Patient disease

Histology was categorized using ICD-0-3 codes: adenocarcinoma (8140, 8250, 8252, 8253, 8255, 8260, 8480, 8481), large cell (8012), squamous (8070, 8071), and mixed or other NSCLC (8000, 8010, 8046, 8560). Stage was limited to advanced stage and was categorized according to American Joint Committee on Cancer (AJCC) staging criteria (IIIB or IV). Grade was categorized as low (grade I or II), high (grade III or IV) or unknown. Primary site was defined as main bronchus (including carina, hilum, bronchus intermedius; C340), lobe (including upper lobe, lingual, apex, and pancoast tumors, C341; middle lobe, C342; lower lobe and base, C343), overlapping lesion of lung (C348), and lung or bronchus, not otherwise specified (NOS; C349). We choose to dichotomize year of diagnosis (prior to 2010 or 2010 and later) and selected a cutoff year prior to the drafting and publication of clinical opinion papers and clinical practice guidelines for molecular testing,[103-105,108,150] assuming some physicians were ordering molecular testing prior to 2010 for research and drug authorization purposes.

Provider characteristics

For each procedure claim, the submitting provider's county of service was documented. Each individual claim was categorized as "in-state" or "out-of-state". Claims billed by providers in SC counties were classified as "in-state" and those submitted by providers not in a SC county were classified as "out-of-state". A patient with at least one claim submitted by an out-of-state provider was classified as out-of-state.

Statistical Analysis

Descriptive statistics for patient and provider characteristics were summarized for the overall cohort and by molecular testing status. Comparisons between molecular testing groups were performed using chi-square tests for categorical variables and a two-sample t-test for age.

Univariate and multivariable logistic regression was used to evaluate the impact of patient and provider characteristics on receipt of molecular testing. Factors included in the final model were identified using backwards elimination followed by forward selection modeling procedures ($p<.05$). Unadjusted and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated.

Kaplan–Meier techniques were used to estimate survival distributions and log-rank tests compared the survival distributions between the molecular testing groups. Univariable Cox proportional hazards regression was used to identify individual prognostic factors predictive of overall survival and multivariable Cox proportional hazards regression was used to evaluate the independent impact of the covariates and molecular testing status on overall survival. Unadjusted and adjusted hazard ratios (HR) and corresponding 95% CIs were estimated.

To reduce potential biases associated with molecular testing on survival, Cox proportional hazards models were estimated using propensity scores. Individual propensity scores were calculated using logistic regression using two separate approaches (non-parsimonious model and parsimonious model). The non-parsimonious model consisted of a logistic regression model using all available covariates, while the parsimonious model contained only variables we found to be significant in our final

multivariable logistic regression model. Next, individual patient propensity scores were calculated based on predicted probabilities from the logistic regression models. Patients who had molecular testing were weighted by the inverse of the probability for getting molecular tested, while patients who did not have molecular testing were weighted by the inverse of the probability for not getting molecular tested. The propensity scores were then used as a covariate to estimate the adjusted effect of molecular testing on survival in the Cox proportional hazards regression models. We then compared the propensity score-adjusted Cox proportional hazards regression models to the model based on independent patient and provider prognostic factors.

All p-values were from two-sided tests and p-values <.05 were considered statistically significant. All analyses were performed with SAS® version 9.4 (SAS Inc., Cary, NC).

Results

A total of 3,842 stage IIIB/IV first primary lung cancer cases were identified during the study period (State Health Plan=341, Medicaid= 3,501). During the same period, 467,832 medical procedure claims from the patients in our cohort were submitted to State Health Plan (115,087) and Medicaid (352,745). Figure 5.1 shows the criteria for patient and claim exclusion. After patient exclusions, 2,266 cases remained eligible for analysis. Of these, 44 cases (1.9%) received molecular testing.

Patient and physician demographics

Table 5.1 details the patient and physician demographic characteristics for the entire study population and by molecular testing subgroup. Mean age at diagnosis was 57.4 years (range: 23-90 years). Males comprised 60.6% of the study population. Over

half of the study population was White (56.9%) and the majority were non-Hispanic (98.0%). The majority of included patients were covered by SC Medicaid (86.0%) and lived in metropolitan counties at the time of diagnosis (75.8%). Similarly, most procedure claims submitted were from in state providers (75.7%). There were no significant differences between those who received molecularly testing and those that did not receive molecularly testing by most demographic characteristics, except for age at diagnosis (p=.002), insurance (p=.007) and provider state (p=.004). Approximately 4% of patients enrolled in SCSEHP received molecular testing, compared to only 1.6% of Medicaid patients. Approximately 2%of patients with in-state only claims received molecular testing, compared to only 0.5% of patients with at least one out of state claim.

Patient disease characteristics

Over 77% of the lung cancer patients in the cohort were diagnosed with stage IV disease. In over half the cases, grade was unknown (60.5%). Adenocarcinoma was the most common histology (37.2%), followed by mixed or other NSCLC (31.0%) and squamous cell carcinoma (23.1%). Lung lobe was the most common disease site (69.5%). Significant differences between molecularly tested and not molecularly tested groups were observed for grade (p=.025) and histology (p<.001). Low-grade patients were more likely to receive molecular testing compared high-grade patients (3.6% vs. 0.9%, respectively). Patients with adenocarcinoma had the highest rate of molecular testing (3.8%) compared to other histologies.

Predictors of molecular testing

Univariable logistic regression identified six individual prognostic factors of having at least one CPT claim for molecular testing. These factors were age at diagnosis,

insurance, provider state, histology, grade, and year of diagnosis (Table 5.2). Most variables that were significant in the univariable models remained independent prognostic factors in the adjusted logistic regression model, except for insurance status (p=0.131, Table 5.3). Similar to the unadjusted models, the adjusted odds of having a molecular test were reduced by 50% for each decade increase in age (OR=0.95, 95% CI: 0.91-0.99, p=.008). Patients with claims submitted by out-of-state providers were about 84% less likely to have molecular testing, after adjustment (OR=0.16, 95% CI: 0.05-0.53, p=.003). Patients with high and unknown grade tumors had reduced odds of having a molecular test compared to patients with low grade tumors (high grade: OR=0.17, 95% CI: 0.06-0.53; unknown grade: OR=0.37, 95% CI: 0.16-0.86; p=.008) after adjustment. Patients with squamous, mixed or other NSCLC, and large cell histologies were all less likely to have molecular testing compared to patients with adenocarcinoma histologies (squamous: OR=0.06, 95% CI: 0.01-0.47; mixed or other NSCLC: OR=0.46, 95% CI: 0.21-1.05; large cell: OR=0.53, 95% CI: 0.15-1.84; p=.015). Patients diagnosed in 2010 or later were over 15 times more likely to having molecular testing compared to patients diagnosed prior to 2010 (OR=15.60, 95% CI: 6.48-37.53, p=<.001).

Molecular testing and overall survival

Median overall survival varied significantly by molecular testing status (log-rank: p<.001; Figure 5.2). Overall survival was longer for patients with molecular testing compared to patients without molecular testing (median=13 vs. 6 months, CI: 8-25 vs. 5-6, respectively). The censoring rate was higher in the molecular testing group compared to the no molecular testing group (27.27% vs 7.83%).

Factors that were individually associated with overall survival included age at diagnosis, insurance, provider state, stage, grade, histology, primary site, year of diagnosis, and molecular testing status. All variables, except grade, remained significant in the multivariable model (Table 5.3). There remained an increased risk of death for each additional decade of age (10%; HR=1.01, 95% CI: 1.00-1.01, p=.004) after adjustment. Patients enrolled in SC Medicaid had an increased risk of death compared to patients enrolled in SCSEHP, once adjusted (HR=1.37, 95% CI: 1.21-1.56, p<.001). Patients who had at least one procedure claim for molecular testing submitted by an out-of-state provider had a 36% reduced risk of death compared to patients whose claims were submitted by an in-state provider (HR=0.64, 95% CI: 0.57-0.71, p<0.001). Stage IV patients had an 83% increased risk of death compared to stage IIIB patients (HR=1.83, 95%CI: 1.64-2.04, p<.001). Patients with mixed or other NSCLC (HR=1.17, 95% CI: 1.05-1.30), large cell carcinoma (HR=1.09, 95% CI: 0.92-1.28), or squamous cell carcinoma (HR=1.12, 95% CI: 1.00-1.26) had increased risk of death compared to those with adenocarcinoma, after adjustment (p=.034). Patients with tumors in the lung and bronchus, not otherwise specified (HR=1.25, 95% CI: 1.11-1.39), overlapping lesions (HR=1.30, 95% CI: 1.00-1.68), or tumors in the main bronchus (HR=1.21, 95% CI: 1.01-1.45) had increased risk of death compared to patients with tumors located in a lung lobe (p<0.001). Patients diagnosed in 2010 or after had a 11% reduced risk of death compared to those diagnosed prior to 2010 (HR=0.89, 95% CI: 0.81-0.99, p=.027).

Once adjusted for age at diagnosis, insurance, provider state, stage, histology, primary site, and year of diagnosis, patients who had molecular testing continued to have

a reduced risk of death compared to patients without molecular testing, although this association was slightly attenuated (HR=0.57, 95% CI: 0.40-0.81, p=.002).

The relationship between molecular testing and overall survival also was adjusted for using propensity scores calculated by both parsimonious and non-parsimonious logistic regression models. Neither model differed greatly from the model based on independent patient and provider prognostic factors. Patients who had molecular testing had a 46% reduced risk of death compared to patients who did not have molecular testing, in both the parsimonious and non-parsimonious models (HR=0.54, 95% CI: 0.38-0.78, p=.001 and HR=0.54, 95% CI: 0.38-0.78, p=.001, respectively; Table 5.4).

Discussion

Overall, this study found a very low rate of molecular testing for patients with advanced NSCLC in SC compared to other studies of *EGFR*-specific testing that reported *EGFR* testing rates between approximately 15-32%.[111-113] Overall, ≈2% of patients in this study received any molecular testing with a higher proportion of patients diagnosed in 2010 or later having molecular testing (5.9%) compared to those diagnosed prior to 2010 (0.37%). This may indicate physician adoption of molecular testing in this population over time, likely as a result of the publication and dissemination of multiple molecular testing guidelines,[103,104,108-110,151] increased integration and ease of molecular testing results in the clinic, and the approval of multiple effective targeted therapies (e.g., gefitinib, erlotinib, and crizotinib) since 2010.[30,116,118]

Several patient and provider factors were predictive of having at least one CPT code for molecular testing. These factors were age at diagnosis, provider state, grade, histology, and year of diagnosis. Our results pertaining to factors associated with having

molecular tests were similar to several other studies.[112,113] A recent study published in 2016 by Enewold and Thomas[112] examined *EGFR* testing only, as opposed to any molecular testing (e.g., *KRAS*, *BRAF*, *ALK*, *ROS1*).[112] Their study found that patients with stage IV lung cancer who were younger, covered by Medicaid, uncovered or had unknown coverage, and diagnosed with large cell and squamous tumors were less likely to have molecular testing, similar to our study results. Shen *et al* also reported younger, as well as female, patients more likely to have molecular testing, similar to our study.[113] Enewold and Thomas also found that *EGFR* testing was also associated with Hispanic/Asian Pacific Islander (API) heritages, marital status, smoking status, having no comorbidities, and living at least two months after cancer diagnosis.[112] We found no relationship between molecular testing and Hispanic ethnicity or marital status and had insufficient information on the other factors. However, our study included few Hispanic and API patients, and thus these results should be interpreted with caution. Patient disease factors that were found to be associated with molecular testing, such as younger age and adenocarcinoma histology, in this study are reported in metastatic NSCLC molecular testing guidelines,[103] suggesting that the early adopters of molecular testing were likely selecting appropriate patients for testing.

We found that molecular testing status was predictive of overall survival. Patients who received molecular testing had a 43% reduced risk of death compared to patients who did not receive molecular testing. Patients with molecular testing also had a longer median survival compared to patients with no molecular testing (13 vs. 6 months, $p<0.001$). Many clinical trials have assessed collectively the impact of molecular testing, presence of a molecular abnormality, and corresponding treatment on overall survival,

but no population-based studies, to our knowledge, have evaluated the impact of broad molecular testing alone on overall survival. Our results suggest that molecular testing alone, may benefit advanced NSCLC patients, presumably due to downstream effects, such as treatment with the best available agent for the patient's tumor molecular profile. Alternately, our finding may indicate that patients who have molecular testing are cared for by providers with greater knowledge about precision medicine, resulting in higher quality care and ultimately longer survival.

Strengths and limitations

Perhaps the biggest limitation to this study is the inability specifically identify the genes analyzed by the ordered molecular tests. This study evaluated patients diagnosed between 2002 and 2012, at which time the practice of code stacking was the only way for physicians to code and bill for molecular testing and *EGFR* testing was predominant. Code stacking is based on method performed, not gene assessed, thus it is impossible for us to know which genes were assessed. Because the patients in this study were diagnosed between 2002 and 2012, however, we acknowledge that most patients were likely tested for abnormalities in the *KRAS* and *EGFR* gene pathways. Additionally, there is the potential for misclassification of molecular testing status. MT status may have been misclassified due to 1) incorrect claim coding, 2) lack of insurance coverage at the time of molecular testing, resulting in the claim not being included in our administrative claims dataset, 3) molecular testing that was covered as part of a clinical trial, 4) molecular testing that was paid by the patient out-of-pocket.

Our cohort consisted of patients with some form of insurance coverage and thus no conclusions can be made for patients with no insurance coverage. Additionally,

patients with Medicare were excluded from this analysis. We may observe fewer patients with molecular testing in cohorts of patients that have no insurance coverage or Medicare, although the latter is likely to be changing as companies that provide multigene molecular testing panels obtain local coverage determinations for their products. As these data were obtained from SCCCR and RFA administrative claims, we also did not have information on several important variables that may impact molecular testing utilization and overall survival, including patient (e.g., socioeconomic status, smoking status, performance status and comorbidities) and provider variables (e.g., specialty, years since medical school graduation, practice setting).

Our assessment of both patient and provider geographic location was limited at the county level. Each provider-submitted claim included information on the county in which the claim originated. Only one county in SC is designated as completely rural by the rural-urban continuum codes and only two counties were designated as nonmetropolitan counties not adjacent to a metropolitan area per United States Department of Agriculture rural-urban continuum codes[152] (used to define rurality in the National Association of Central Cancer Registries). Thus, no molecular testing claims in this dataset were submitted in the rural setting. As such, we assessed the provider geographic location variable as "in state" versus "out of state". Only 3 molecular tests were performed out of state, thus conclusions on the impact of provider geographic location must be interpreted with caution.

While our analyses had some limitations, a strength of the study was the ability to provide an early assessment of the factors impacting molecular testing utilization based on the only CPT codes available to track molecular testing at the time. Another strength

of this study is its ability to assess the impact of molecular testing alone on overall survival, an evaluation typically performed in clinical trials and in conjunction with molecular test results. Finally, use of SCCCR and RFA administrative claims data allowed us to assess these outcomes across a wide geographic area and with a large number of cases. Approximately one-third of SC's population is rural. Few academic medical centers and only one National Cancer Institute designated cancer center is located in SC, making this assessment of particular importance. Prior research indicates disparities between academic and community-based provider knowledge and understanding of molecular testing.[101]

Conclusions

Several disease characteristics were found to be associated with increased molecular testing utilization in patients with advanced NSCLC, and molecular testing had a positive impact on overall survival. Future research could evaluate more recent data using the 2013 revised Tier 1 (gene specific; 81200-81383) and Tier 2 (molecular pathology; 81400-81408) codes and could consider various methods of molecular testing (e.g., tumor versus liquid biopsies). Assessment of provider-level variables affecting these outcomes, such as geographic location, should be further investigated in national datasets, such as the Surveillance, Epidemiology, and End Results-Medicare data. Larger, more geographically diverse national datasets will provide more detailed data on both providers and patients.

Tables and Figures

Table 5.1. Patient, physician, and disease characteristics for the overall population and molecular testing subgroups

	All Patients (N, %)		Molecular Test - Yes (N, %)		Molecular Test - No (N, %)		P value
	2266	**100**	**44**	**1.94**	**2222**	**98.06**	-
Patient/Provider Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	-
Age at Diagnosis (years)							0.002*
Mean (SD)	57.4		53.0		57.5		
Median	57.4		54.5		57.0		
Range	23.0-90.0		32.0-71.0		23.0-90.0		
Age at Diagnosis (years)							0.066
<52	608	26.8	17	38.6	591	26.6	
52-57	571	25.2	14	31.8	557	25.1	
58-62	523	23.1	8	18.2	515	23.2	
63+	564	24.9	5	11.4	559	25.1	

Sex							0.438
Male	1372	60.6	24	54.6	1348	60.7	
Female	894	39.5	20	45.5	874	39.3	
Race							0.181
White	1289	56.9	29	65.9	1260	56.7	
Black	953	42.1	14	31.8	939	42.3	
Other	24	1.0	1	2.3	23	1.0	
Hispanic							0.590
Non-Hispanic	2221	98.0	43	97.7	2178	98.0	
Hispanic	23	1.0	1	2.3	22	1.0	
Unknown	22	1.0	0	0.0	22	1.0	
Marital Status							0.120
Not married	1203	53.1	23	52.3	1180	53.1	
Married	690	30.5	18	40.9	672	30.2	
Unknown	373	16.4	3	6.8	370	16.7	
Insurance							0.007*

State health plan	318	14.0	13	29.6	305	13.7	
Medicaid	1948	86.0	31	70.4	1917	86.3	
Patient Metropolitan Status							>0.999
Non-metropolitan/rural	549	24.2	10	22.7	539	24.3	
Metropolitan	1717	75.8	34	77.3	1683	75.7	
Provider State							0.004*
Out of state	551	24.3	3	6.8	548	24.7	
In state	1715	75.7	41	93.2	1674	75.3	
Disease Characteristics							
AJCC Stage							0.587
IIIB	517	22.8	8	18.1	509	22.9	
IV	1749	77.2	36	81.82	1713	77.1	
Grade							0.025*
Low	250	11.0	9	20.45	241	10.8	
High	646	28.5	6	13.64	640	28.8	
Unknown	1370	60.5	29	65.91	1341	60.4	

Histology							<.001*
Adenocarcinoma	842	37.2	32	72.73	810	36.5	
Large cell	196	8.7	3	6.82	193	8.7	
Squamous	524	23.1	1	2.27	523	23.5	
Mixed or other NSCLC	704	31.0	8	18.18	696	31.3	
Primary Site							0.385
Main bronchus	140	6.2	1	2.27	139	6.3	
Lobe	1575	69.5	36	81.82	1539	69.3	
Overlapping lesion	62	2.7	1	2.27	61	2.8	
Lung and bronchus, NOS	489	21.6	6	13.64	483	21.7	
Year of Diagnosis							<.0001*
Prior to 2010	1619	71.5	6	13.6	1613	72.6	
2010 or later	647	28.5	38	86.4	609	27.4	

Abbreviations: N, number; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; SD, standard deviation
*Significant at the $p \leq 0.05$ level.

Table 5.2. Univariable and multivariable logistic regression results for molecular testing

	Univariable Logistic Regression			Multivariable Logistic Regression		
	Unadjusted OR	**95% CI**	**P value**	**Adjusted OR**	**95% CI**	**P value**
Patient/Provider Characteristics						
Age at Diagnosis (years)	0.95	0.92-0.98	0.002*	0.95	0.91-0.99	0.008*
Sex			0.412			
Male	Reference					
Female	1.29	0.71-2.34				
Race			0.314			
White	Reference					
Black	0.65	0.34-1.23				
Other	1.89	0.25-14.47				
Hispanic			0.722			
Non-Hispanic	Reference					
Hispanic	2.30	0.30-17.47				
Unknown	<0.001	<0.01->999.99				

Marital Status			0.146			
Not married	Reference					
Married	1.37	0.74-2.57				
Unknown	0.416	0.12-1.39				
Insurance			0.004*			
State health plan	Reference					
Medicaid	0.38	0.20-0.73				
Patient Metropolitan Status			0.82			
Non-metropolitan/rural	0.92	0.45-1.87				
Metropolitan	Reference					
Provider State			0.013*			0.003*
Out of state	0.22	0.07-0.73		0.16	0.05-0.53	
In state	Reference			Reference		
Disease Characteristics						
AJCC Stage			0.461			
IIIB	Reference					

IV	1.34	0.62-2.89				
Grade			0.034*			0.008*
Low	Reference			Reference		
High	0.25	0.09-0.71		0.17	0.06-0.53	
Unknown	0.58	0.27-1.24		0.37	0.16-0.86	
Histology			<0.001*			0.015*
Adenocarcinoma	Reference			Reference		
Large cell	0.39	0.12-1.30		0.53	0.15-1.84	
Squamous	0.05	0.01-0.36		0.06	0.01-0.47	
Mixed or other NSCLC	0.29	0.13-0.64		0.46	0.21-1.05	
Primary Site			0.357			
Main bronchus	0.31	0.04-2.26				
Lobe	Reference					
Overlapping lesion	0.70	0.10-5.20				
Lung and bronchus, NOS	0.53	0.22-1.27				
Year of Diagnosis			<0.001*			<.001*

Prior to 2010	Reference			Reference		
2010 or later	16.77	7.06-39.88		15.60	6.48-37.53	

Abbreviations: CI, confidence interval; N, number; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OR, odds ratio
Note: Only significant variables were included in the final model.
*Significant at the p≤0.05 level.

Table 5.3. Univariable and multivariable Cox proportional hazards regression for overall survival

	Univariable Cox Proportional Hazards Regression			**Multivariable Cox Proportional Hazards Regression**		
	Unadjusted HR	**95% CI**	**P value**	**Adjusted HR**	**95% CI**	**P value**
Patient/Provider Characteristics						
Age at Diagnosis (years)	1.01	1.01-1.01	<0.001*	1.01	1.01-1.01	0.004*
Sex			0.091			
Male	Reference			Reference		
Female	0.93	0.85-1.01				
Race			0.548			
White	Reference			Reference		
Black	0.96	0.88-1.04				
Other	0.91	0.59-1.38				

Hispanic			0.167			
Non-Hispanic	Reference			Reference		
Hispanic	0.73	0.46-1.16				
Unknown	1.34	0.87-2.06				
Marital Status			0.124			
Not married	Reference					
Married	0.90	0.82-1.00				
Unknown	0.96	0.85-1.09				
Insurance			0.003*			<0.001*
State health plan	Reference			Reference		
Medicaid	1.21	1.07-1.37		1.37	1.21-1.56	
Patient Metropolitan Status			0.922			
Non-metropolitan/rural	1.01	0.91-1.11				
Metropolitan	Reference					
Physician State			<0.001*			<0.001*
Out of state	0.68	0.61-0.75		0.64	0.57-0.71	

In state	Reference			Reference		
Disease and Molecular Testing Characteristics						
AJCC Stage			<0.001*			<0.001*
IIIB	Reference			Reference		
IV	1.76	1.58-1.95		1.83	1.64-2.04	
Grade			0.002*			
Low	Reference					
High	1.29	1.10-1.51				
Unknown	1.29	1.12-1.49				
Histology			0.001*			0.034*
Adenocarcinoma	Reference			Reference		
Large cell	1.16	0.99-1.36		1.09	0.92-1.28	
Squamous	1.08	0.97-1.21		1.12	1.00-1.26	
Mixed or other NSCLC	1.23	1.11-1.36		1.17	1.05-1.30	
Primary Site			<0.001*			<0.001*

Main bronchus	1.20	1.01-1.44		1.21	1.01-1.45	
Lobe	Reference			Reference		
Overlapping lesion	1.30	1.00-1.68		1.30	1.00-1.68	
Lung and bronchus, NOS	1.33	1.20-1.48		1.25	1.12-1.39	
Year of Diagnosis			0.005*			0.027*
Prior to 2010	Reference			Reference		
2010 or later	0.87	0.79-0.96		0.89	0.81-0.99	
Molecular Testing			<0.001*			0.002*
Yes	0.53	0.37-0.75		0.57	0.40-0.81	
No	Reference			Reference		

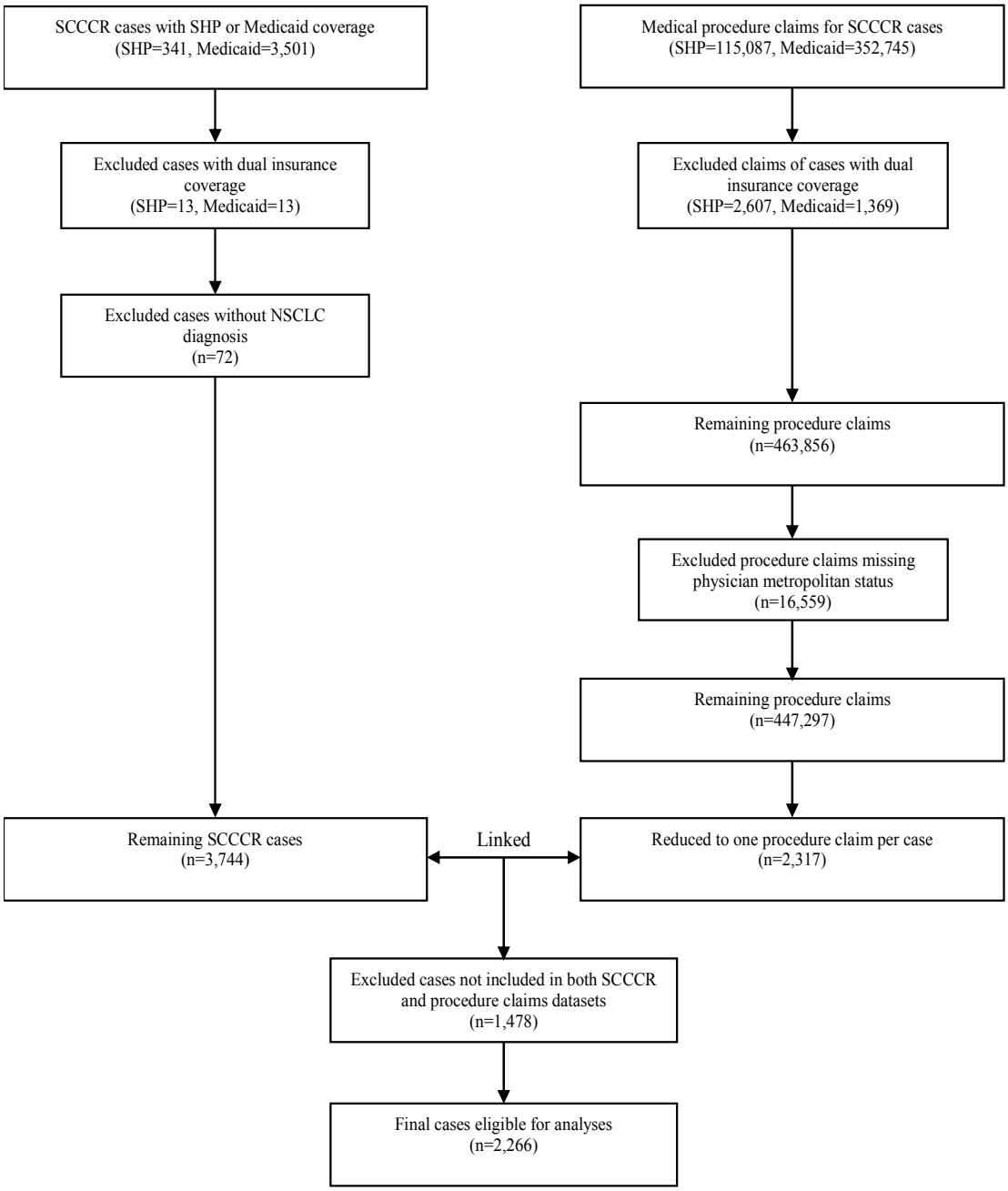
Abbreviations: CI, confidence interval; HR, hazards ratio; N, number; NOS, not otherwise specified; NSCLC, non-small cell lung cancer

*Only significant variables ($p \leq 0.05$) were included in the final model.

Table 5.4. Comparison of adjustment methods estimating the impact of molecular testing on overall survival

	Comparison of Adjusted Cox Proportional Hazards Regression Methods		
Method	**Adjusted HR**	**95% CI**	**P value**
Cox PH model	0.57	0.40-0.81	0.002*
Propensity score, parsimonious	0.54	0.38-0.78	0.001*
Propensity score, non-parsimonious	0.54	0.38-0.78	0.001*

Abbreviations: CI, confidence interval; HR, hazards ratio; PH, proportional hazards
*Significant at the $p \leq 0.05$ level.



Abbreviations: NSCLC, non-small cell lung cancer; SCCCR, South Carolina Central Cancer Registry; SHP, State Health Plan

Figure 5.1. Lung cancer registry case and corresponding claim(s) inclusion and exclusion

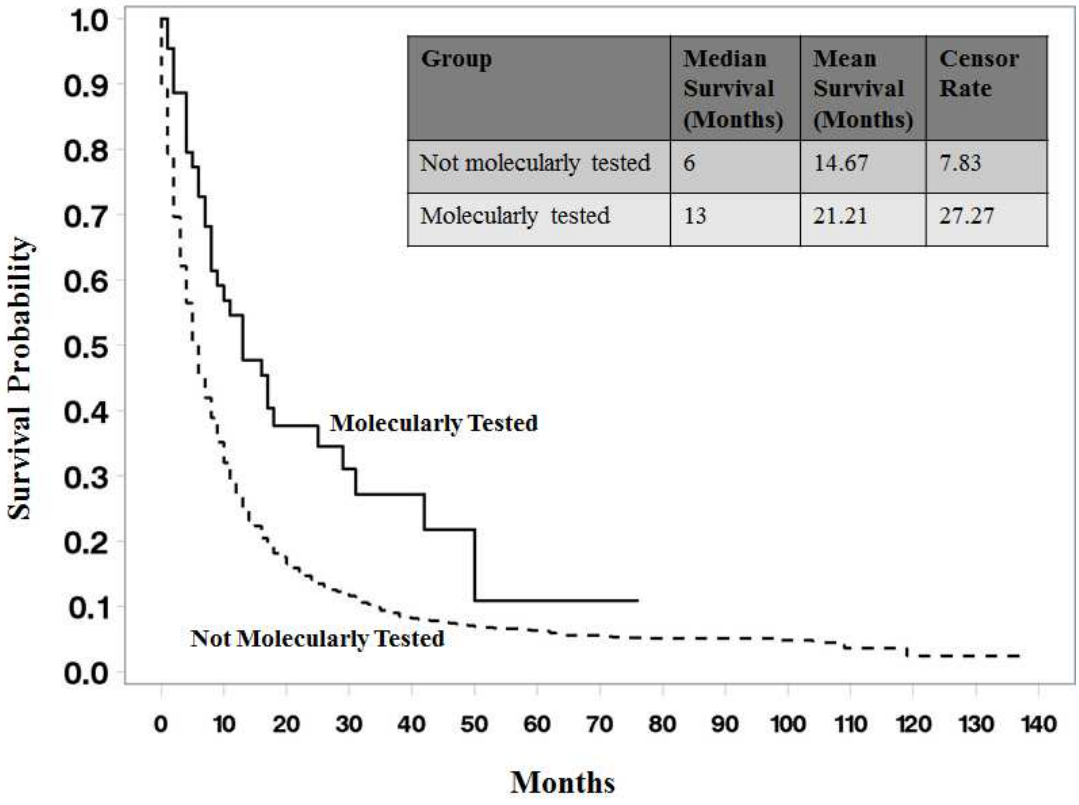


Figure 5.2. Overall survival for lung cancer patients, stratified by molecular testing status

CHAPTER VI:

PREDICTORS OF ERLOTINIB UTILIZATION AND THE IMPACT OF ERLOTINIB USE ON OVERALL SURVIVAL IN ADVANCED, NON-SMALL CELL LUNG CANCER: A RETROSPECTIVE COHORT STUDY[3]

[3] Ersek JL, Symanowski J, Kim ES, Adams SA, Eberth JM. To be submitted to Journal of Thoracic Oncology.

Abstract

Introduction: Epidermal growth factor receptor (*EGFR*)-directed therapies are approved for selected patients with non-small cell lung cancer (NSCLC); however, little information on predictors of utilization and efficacy in the population-based setting has been reported. We aimed to identify predictors of early erlotinib prescribing and evaluate the impact of erlotinib on survival in patients diagnosed with stage IIIB/IV NSCLC residing in South Carolina (SC).

Methods: SC Central Cancer Registry cases diagnosed between January 1, 2002 and December 31, 2012 were linked to SC State Employee Health Plan (SCSEHP) and Medicaid administrative claims data. Logistic regression (LR) was used to identify predictors of erlotinib utilization. Kaplan-Meier methods were used to estimate survival distributions and log-rank tests compared the survival distributions between erlotinib groups. Cox proportional hazards (PH) modeling was used to assess the impact of patient demographic, disease, and treatment characteristics on survival, while adjusting for other prognostic covariates. Multivariable LR models were used to estimate propensity scores, which were then used as covariates in adjusted Cox PH models.

Results: A total of 1,623 patients were eligible. Independent predictive factors for having at least one erlotinib claim, included younger age at diagnosis (p=.004), female sex (p=.048), SCSEHP (p<.001), out-of-state providers (p<.001), adenocarcinoma histology (p<.001), and having molecular testing (p=.018). Overall survival (OS) was longer for patients who received erlotinib (median OS=14 versus 7 months, p<0.001). After adjustment for significant prognostic factors, patients who received erlotinib had a 35%

reduced risk of death compared to patients with no erlotinib (HR=0.65, 95% CI: 0.56-0.75, p<.001).

Conclusions: Several factors were associated with erlotinib utilization and disparities in access may exist. Erlotinib utilization was associated with a reduced risk of death in patients with NSCLC in SC.

Introduction

Lung cancer is the leading cause of cancer-related death in the United States and in South Carolina.[1,145] In 2017, approximately 4,320 new lung cancer cases will be diagnosed and 2,920 lung cancer deaths will occur.[1] Most lung cancer patients are diagnosed with advanced disease and the overall 5-year survival rate is 18%.[1] Until recently, patients with advanced, non-small cell lung cancer have mostly been treated with platinum-based chemotherapy doublets or pemetrexed. None of these systemic regimens have demonstrated significant improvement in long-term response or survival.[4,146]

Recently, advances in the genomic profiling (or molecular testing) of tumors have identified multiple alterations in lung tumors that can be targets for treatment, providing personalized targeted and immunotherapy options for patients with specific molecular abnormalities. For example, epidermal growth factor receptor (*EGFR*) is a cell surface receptor that is activated either by protein overexpression, increased gene copy number or genetic mutation. *EGFR* is involved with cell proliferation, suppression of apoptosis (cell death), cell motility, invasion and angiogenesis (formation of new blood vessels).[20,25] Patients whose tumors harbor *EGFR* mutations can be treated with one of several *EGFR* tyrosine kinase inhibitors (TKIs), including gefitinib, erlotinib, and afatinib,[116-118] which

have demonstrated increased tumor response rates and median progression-free survival and decreased toxicity in clinical trial patients.[6,7,9,10,121,153] Prior to Food and Drug Administration (FDA) approval, clinical investigators and treating physicians identified several patient characteristics that appeared to be associated with response and therefore would benefit patients receiving *EGFR* TKI therapy. As reported at annual oncology meetings and in early publications, these characteristics included female sex, Asian race, adenocarcinoma histology, and never-smoking history.[92,94,122,154-156]

In 2003, gefitinib was the first EGFR TKI to gain FDA accelerated approval for use as monotherapy in patients with advanced non-small cell lung cancer after failure of platinum-based and docetaxel regimens.[157] Just two years later, in 2005, gefitinib was restricted to use in patients currently or previously benefiting from gefitinib and/or patients participating in clinical trials on the basis of failure to show improvement in outcomes.[158,159]

Around the same time (2004), the FDA approved erlotinib for use in patients in the similar, unselected patient population and erlotinib eventually gained approval in the maintenance setting (i.e., following stable or response after 4-6 cycles of first-line platinum-based chemotherapy) in 2010. 'Unselected' means the use of the drug is not informed by a patient's *EGFR* mutation status. In 2013, the FDA revised the indication to restrict erlotinib use to a selected patient population, making it available in the first-line setting for patients with metastatic NSCLC whose tumors harbored selected *EGFR* mutations (exon 19 deletion or exon 21 L858R mutated). Erlotinib remained an option for second-line therapy and beyond in the unselected population. While progression-free survival and toxicity outcomes across phase III clinical trials of erlotinib have been

positive with regards to response, only small increases in overall survival (1-2 months) have been observed in the unselected population.[11,29,132] Additionally, in a recent study by Enewold and Thomas using population-based data, no association between erlotinib and survival was reported.[112]

Treatment of metastatic NSCLC continues to evolve at a rapid pace. Little research has evaluated erlotinib in patients with NSCLC outside of the clinical trial setting.[112,114] The purpose of this study was to determine factors associated with whether or not a patient received the *EGFR* TKI targeted therapy, erlotinib, among patients with advanced NSCLC residing in South Carolina and to determine if erlotinib use improved overall survival in the population-based setting.

Methods

Study Design, Data Source, and Cohort Selection

We linked outpatient drug and procedure claims data from the South Carolina (SC) Revenue and Fiscal Affairs (RFA) administrative claims to eligible cases in the South Carolina Central Cancer Registry (SCCCR) to retrospectively evaluate erlotinib utilization and overall survival. Eligible cases were those included in the SCCCR diagnosed with stage IIIB/IV lung cancer between January 1, 2002 and December 31, 2012, were enrolled in South Carolina State Employee Health Plan (SCSEHP) or SC Medicaid during the study period, and had at least one procedure and one drug claim. Patients with dual insurance coverage, HMO coverage, Medicare as the primary payer, and patients with no insurance were not included in this study.

Outcomes

Erlotinib utilization was determined using National Drug Codes (NDC) from drug administrative claims. Patients with at least one claim for erlotinib, using one of the following NDC codes, were classified as "yes": '54868-5447-0', '54868-5474-0', '69189-0063-1', '50242-062-01', '50242-063-01', '50242-064-01', or '54868-5290-0'. Erlotinib claims were for any line of therapy. Patients with all other NDC codes were classified as not utilizing erlotinib. We assume that having at least one claim for erlotinib resulted in utilization of the drug. Overall survival was calculated from the date of primary lung cancer diagnosis to the date of death for deceased cases. Surviving cases were censored at the date of last follow-up or December 31, 2014.

Covariates

Patient and provider demographics

Sex was categorized as male or female. Age at diagnosis was evaluated as both a continuous and as a categorical variable (<52, 52-57, 58-62, 63+ years). Race was categorized as White, Black, or other. Hispanic ethnicity was categorized as Hispanic, non-Hispanic, or unknown. Marital status was categorized as married, not married, or unknown. Patient metropolitan status was derived using rural-urban continuum codes assigned to each patient's county and were ultimately dichotomized as non-metropolitan versus metropolitan.[152] Non-metropolitan included rural counties.

Data on provider geographic location was not available for the drug claims, thus we used provider geographic location for molecular testing (obtained through procedure claims) as a proxy for drug claim provider geographic location. Procedure claims contained information on provider geographic location, specifically county, for each

claim submitted. All providers with procedure claims submitted in a SC county were categorized as 'in state', while providers with procedure claims submitted outside of SC were categorized as 'out of state'.

Patient disease

Cases with the following ICD-0-3 codes were included in this study: adenocarcinoma (8140, 8250, 8252, 8253, 8255, 8260, 8480, 8481), large cell (8012), squamous (8070, 8071), and mixed or other NSCLC (8000, 8010, 8046, 8560). Small cell lung cancer cases were excluded. Stage was limited to advanced stage and was categorized according to American Joint Committee on Cancer (AJCC) staging criteria as stage IIIB or IV. Grade was categorized as low (grade 1 or 2), high (grade 3 or 4) or unknown. Primary site was defined as main bronchus (including carina, hilum, bronchus intermedius; C340), lobe (including upper lobe, lingual, apex, and pancoast tumors, C341; middle lobe, C342; lower lobe and base, C343), overlapping lesion of lung (C348), and lung or bronchus, not otherwise specified (NOS; C349). Year of diagnosis was defined as prior to 2010 and 2010 or later. 2010 was selected as the cutoff year as this was the first year that erlotinib was approved as maintenance treatment for patients with locally advanced or metastatic NSCLC whose disease had not progressed after four cycles of first-line platinum-based chemotherapy regimen (or in other words, available in the first line setting). Additionally, 2010 was just prior to the publication of many lung cancer guidelines supporting the use of molecular testing and targeted therapy approaches.[103-105,108,150] Molecular testing was determined using Common Procedure Terminology codes and included any molecular tests performed. Cases with molecular

testing method codes (83890-83914) were categorized as 'yes'. These include both *EGFR* specific and multigene testing.

Statistical Analysis

Patient demographic and disease characteristics were summarized for the overall cohort and by erlotinib use. Age was summarized as a continuous and a categorical variable. Frequencies and percentages were reported for all other variables. Comparisons between erlotinib groups were performed using chi-square tests for categorical variables and a two-sample t-tests for age.

Univariable and multivariable logistic regression was used to evaluate the impact of patient and provider characteristics on erlotinib utilization. Factors included in the final multivariable model were identified using backwards elimination followed by forward selection modeling procedures to confirm variables identified using backward elimination. All variables significant at the $p<.05$ level were retained in the final model. Odds ratios (OR), corresponding 95% confidence intervals (CI) and p-values were estimated.

Kaplan–Meier techniques were used to estimate survival distributions and log-rank tests compared the distributions between the erlotinib groups. Univariable Cox proportional hazards regression was used to identify individual prognostic factors predictive of overall survival. Multivariable Cox proportional hazards regression was used to evaluate the independent impact of the covariates and erlotinib use on overall survival. Hazard ratios (HR) and corresponding 95% CIs were estimated.

Propensity scores were estimated to reduce potential biases associated with erlotinib use on overall survival and were included in separate Cox proportional hazards

models. Two logistic regression models were estimated to calculate the predicted probability of erlotinib use (non-parsimonious and parsimonious). The non-parsimonious model included all 13 available covariates and the parsimonious model included only covariates found to be significant in our final multivariable logistic regression model. Individual propensity scores (weighted probabilities) were calculated based on predicted probabilities from the logistic regression models. Patients who received erlotinib were weighted by the inverse of the probability for getting erlotinib, while patients who did not have molecular testing were weighted by the inverse of the probability for not getting erlotinib. The propensity score was then used as a covariate in the Cox proportional hazards regression models to estimate the adjusted effect of erlotinib utilization on survival. We then compared the propensity score-adjusted Cox proportional hazards regression models to traditional multivariable models. The results of the two propensity score-adjusted models were then compared to the model based on independent patient and provider prognostic factors.

All hypothesis testing was 2-sided with a $p<0.05$ level of statistical significance. The SAS statistical package V9.4 was used for data analyses (SAS Inc., Cary NC).

Results

A total of 1,623 cases met eligibility criteria and had at least one claim in both the procedures and drug claims datasets. 54,897 Medicaid and 19,533 SHP drug claims were used to categorize erlotinib use. 18.4% of patients were members of the SCCEHP, while 81.6% were enrolled in SC Medicaid. Of all eligible cases, 14.0% had at least one claim for erlotinib and 1,396 (86.0%) had no erlotinib claims (Table 6.1). Figure 6.1 outlines

lung cancer registry case and corresponding procedure and drug claims inclusion and exclusion criteria.

Patient and provider demographics

For the overall cohort, mean age at diagnosis was 56.8 years (Median=57, Range: 23-90). A higher proportion of patients were male, White, and non-Hispanic (58.9%, 58.1%, and 98.3%, respectively). About half of the patients were not married (51.0%) and the majority had Medicaid insurance (81.6%). Most patients lived in metropolitan areas at the time of diagnosis (75.4%). Provider state was most often in-state (70.0%). Marital status, insurance, and provider state differed significantly by erlotinib status ($p=0.004$, $p<0.001$, and $p=0.0345$, respectively). The rate of erlotinib utilization was higher for patients who were married, had SCSEHP coverage, and had at least one encounter with an out-of-state provider.

Patient disease characteristics

Most patients were stage IV at the time of diagnosis (75.9%). Adenocarcinoma histology was most frequent (37.4%) followed by mixed or other NSCLC (29.8%), squamous (24.0%) and large cell (8.8%). The majority of tumors were located in a lung lobe (71.2%). Only 2.5% of patients received any molecular testing. Histology ($p<.001$) and molecular testing ($p=.002$) varied significantly by erlotinib status, with a higher proportion of adenocarcinomas and patients with a molecular testing claim received erlotinib (55.1% and 5.7%, respectively).

Predictors of erlotinib utilization

Results from univariable analyses are presented in Table 6.2. Individual significant predictors of erlotinib use were age of diagnosis ($p=.001$), sex ($p=.010$),

marital status (p=.004), insurance (p<.001), provider state (p=.031), histology (p<.001), and molecular testing (p=.001).

In the adjusted logistic regression models, most variables remained significant predictors of erlotinib use, with the exception of marital status (p=0.322; Table 6.2). For each increasing decade, the odds of erlotinib utilization were reduced by 30%, (OR=0.97, 95% CI: 0.96-0.99, p=.004). Patients with Medicaid and non-adenocarcinoma histologies also had reduced odds of receiving erlotinib compared to patients with SCSEHP (OR=0.29, 95% CI: 0.20-0.42, p<.001) and adenocarcinoma histologies (mixed/other NSCLC OR=0.64, 95% CI: 0.46-0.91, squamous OR=0.36, 95% CI: 0.29-0.68, large cell OR=0.28, 95% CI: 0.13-0.60, p<.001). Patients with at least one claim submitted by an out-of-state provider were over two times more likely to receive erlotinib compared to patients with only in-state claims (OR=2.03, 95% CI: 1.43-2.89, p<0.001). Lastly, female patients and patients with molecular testing were more likely to receive erlotinib compared to males and patients without molecular testing (OR=1.35, 95%CI: 1.00-1.81, p=0.048 and OR=2.37, 95% CI: 1.16-4.85, p=0.018, respectively).

Erlotinib and overall survival

Overall survival for patients with erlotinib claims was longer than for patients with no erlotinib claims (median OS=14 versus 7 months, p<0.001; Figure 6.2). The censoring rate was slightly higher in the erlotinib group (10.13%) compared to the no erlotinib group (9.31%).

Seven covariates were found to be predictors of overall survival. Univariable HRs and corresponding 95% CIs are presented in Table 6.3. Significant covariates

included age at diagnosis (p<.001), provider state (p<.001), stage (p<.001), grade (p=.005), primary site (p=.001), molecular testing (p=.005), and erlotinib use (p<.001).

Age at diagnosis, provider state, stage, primary site, year of diagnosis, molecular testing, and erlotinib use all remained significant predictors of overall survival in the multivariable analysis (Table 6.3). Grade no longer remained significant (p=0.126), however, year of diagnosis was a significant predictor of overall survival in the multivariable model. A 10% increase in the risk of death was observed for each additional decade of life (HR=1.01, 95% CI: 1.00-1.01, p<.007). Patients with at least one claim submitted by an out-of-state provider had a 24% reduced risk of death compared to patients with only in-state claims (HR=0.76, 95% CI: 0.68-0.85, p<.001). As expected, patients diagnosed with stage IV disease had an increased risk of death compared to those diagnosed with stage IIIB (HR=1.96, 95% CI: 1.73-2.23, p<.001). Patients with a primary site of disease outside the lung lobe (main bronchus, overlapping lesions, and lung/bronchus NOS) also saw an increased risk of death compared to patients with a primary site of lung lobe (HR=1.20, 95% CI: 0.96-1.48, HR=1.36, 95% CI: 1.02-1.84, OR=1.18, 95% CI: 1.04-1.35, p=.010, respectively). Patients diagnosed prior to 2010 had a reduced risk of death compared to patients diagnosed in 2010 or later (HR=0.87, 95% CI: 0.77-0.98, p=.020).

The risk of death for patients with molecular testing and for patients with erlotinib claims did not largely change from the univariable model. Reduced risk of death was still observed for those with molecular testing and erlotinib claims. The adjusted results showed patients with molecular testing had 35% reduced risk of death compared to patients with no molecular testing (HR=0.65, 95% CI: 0.45-0.95, p=.024). Patients with

at least one erlotinib claim also had a 35% reduced risk of death compared to patients with no erlotinib claims (HR=0.65, 95% CI: 0.56-0.75, p<.001).

Propensity score adjusted hazards

Propensity scores were calculated using multivariable logistic regression to estimate the propensity for erlotinib given a set of covariates. Using weighted propensity scores (inverse probability of treatment weights; IPTW) as a method of adjustment increased the reduction in the risk of death in both scenarios. For the non-parsimonious (all available covariates) and parsimonious models (variables deemed significant using multivariable logistic regression), the risk of death was reduced by 41% and 43%, respectively (HR=0.59, 95% CI: 0.48-0.73, p<0.001; HR=0.57, 95% CI: 0.46-0.71, p<0.001), which was generally consistent with the adjusted results from the individual covariate model (Table 6.4).

Discussion

Treatment for advanced stage, NSCLC is rapidly evolving. Targeted therapies have delivered on increasing survival and decreasing toxicity in patients who otherwise would have been treated with platinum-based chemotherapies. Our study assessed predictors of targeted therapy (erlotinib) utilization and overall survival in a population-based setting during the time period when erlotinib was only approved for use in unselected patients with locally advanced or metastatic NSCLC. We found several factors associated with increased odds of receiving any line erlotinib treatment, including female sex, having at least one procedure claim submitted by an out of state provider, and having any molecular testing. Our findings that females were more likely to receive erlotinib are in alignment with results from recently published data evaluating the use of

EGFR-specific molecular testing in 2012-2014 using MarketScan data, published by Shen *et al*.[113] These data also support the early clinical observations that responses to drugs, such as erlotinib, were more likely in specific patient demographic cohorts, including that of females.

The current study found a low rate of molecular testing overall (2.5%). While erlotinib did not receive a FDA indication for use exclusively in patients with *EGFR* mutated tumors until 2013, the link between *EGFR* mutation and benefit of drugs such as erlotinib and gefitinib was described as early as 2004.[92,94] Additionally, there were early discussions of the clinical characteristics of patients more likely to benefit from *EGFR* therapy even before the *EGFR* mutation relationship was confirmed. Thus, early prescribers of erlotinib were likely aware of the rapidly evolving scientific literature surrounding this class of drugs.

We found that patients were more likely to have treatment with erlotinib if they had at least one procedure claim submitted by an out-of-state provider, however, this result should be interpreted with caution for several reasons. First, we used a proxy variable for provider state based on molecular testing procedure claims. We presumed that if a patient travelled outside SC for molecular testing, they likely travelled outside SC to receive treatment. Additionally, evaluation of molecular testing procedure claims identified only three patients with molecular testing claims from an out-of-state provider, thus, this result is based on very small numbers. Shen *et al* reported that geographic region may influence *EGFR* testing, with patients diagnosed in the Western United States more likely to have *EGFR* testing.[113]

We also reported several factors associated with decreased odds of having at least one erlotinib claim including increasing age, Medicaid insurance, and non-adenocarcinoma histology. We found an approximately 26% decreased risk of receiving erlotinib for each decade of life. Our result was similar to the inverse association (although non-significant) between age and erlotinib observed in a recent study.[112] Younger patients may be more likely to be prescribed erlotinib for several reasons. They may be more suitable for therapy overall and thus more likely to receive multiple lines of therapy, increasing the likelihood of receiving erlotinib in the second-line setting and beyond. Younger patients may also be more motivated to research and explore cutting-edge, novel therapies on their own and bring discussion of these options to their physicians. Also, for working younger patients, an oral therapy, such as erlotinib, may be more accommodating to their lifestyles than an IV chemotherapy regimen. Our result that patients with non-adenocarcinoma history are less likely to be prescribed erlotinib is similar to the Enewold and Thomas study and is likely to reflect the early use of clinical characteristics in selection of appropriate patients by oncologists. Enewold and Thomas also found patients with Medicaid coverage less likely to receive erlotinib,[112] similar to our results. Patients with Medicaid in our study were about 70% less likely to be prescribed erlotinib compared to patients enrolled on SCSEHP. Patients with SCSEHP coverage are likely to be higher SES, compared to Medicaid patients, and may be more likely to have the resources to cover off-label copays. Additionally, SCSEHP plans may have been more accommodating of off-label drug use requests.

Our results show a reduced risk of death for patients who received erlotinib and for patients who had molecular testing regardless of *EGFR* mutation status. Patients who

were treated with erlotinib had a 7-month increase in median OS compared to patients with no erlotinib claims. This study evaluated erlotinib use early in its approval history. Patients who received erlotinib early on may have received this drug as part of a clinical trial, which may explain the similar survival length for patients in this study and patients in unselected clinical trials.[128,129,132]

Limitations and Strengths

While we had information on some of the demographic and clinical characteristics associated with increased response to erlotinib, which may impact likelihood of erlotinib prescribing, we were lacking information on other important characteristics identified through previous research, including never smoking status and Asian race.[92,94,160] We were also unable to assess line of therapy (e.g., first, subsequent) in which erlotinib was administered. Additionally, we did not have information on the provider geographic location for which the erlotinib claim was submitted and used provider location for molecular testing as a proxy variable.

One strength of this study is that it included patients documented in a state-wide cancer registry. This sample allowed us to evaluate predictors of erlotinib and its impact on survival in a diverse group of cancer patients coming from a variety of different treatment centers (e.g., academic, community-based). Additionally, this is the first study to our knowledge to use IPTW propensity scores as an adjustment method for controlling for baseline covariates in analyses of erlotinib survival. We found this method to result in a similar, although slightly reduced, risk of death compared to other adjustment methods where individual covariates were included in the model. Correcting imbalance in baseline covariates in observational studies through the use of IPTW propensity scores

as covariates appears to be a useful strategy for adjustment in samples of diverse cancer registry patients.

Conclusions

Development, approval, and clinical use of targeted and immuno therapies is rapidly changing the treatment of patients with NSCLC. Despite education attempts, the adoption of molecular testing and precision medicine utilization are low in South Carolina. Reasons for this include the high costs of molecular tests that are needed to guide therapy decisions and the complexity of interpreting molecular reports. As precision medicine becomes an increasingly major component of lung cancer diagnosis and treatment, providers must find ways to keep abreast of evolving scientific literature and new molecular discoveries. The use of clinical decision support tools and involvement on molecular tumor boards is encouraged.

This study identified several non-clinical disparities in utilization of erlotinib, including insurance type, that should be further examined. Additionally, we found a reduced risk of death for patients treated with erlotinib. Future research could explore the impact erlotinib on survival in among patients with and without *EGFR* mutation in the population-based setting using national datasets.

Tables and Figures

Table 6.1. Patient, physician, and disease characteristics for the overall population and erlotinib subgroups

	All Patients (N, %)		Erlotinib (N, %)		No Erlotinib (N, %)		P-value
	1623	**100**	**227**	**13.99**	**1396**	**86.01**	-
Patient/Physician Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	-
Age at Diagnosis (years)							0.001*
Mean (SD)	56.8		54.9		57.1		
Median	57.0		56.0		57.0		
Range	23-90		30-80		23-90		
Age at Diagnosis (years)							0.008*
<52	452	27.9	71	31.3	381	27.3	
52-57	420	25.9	70	30.8	350	25.1	
58-62	385	23.7	53	23.4	332	23.8	
63+	366	22.6	33	14.5	333	23.9	
Sex							0.011*

Male	956	58.9	116	51.1	840	60.2	
Female	667	41.1	111	49.0	556	39.8	
Race							0.701
White	943	58.1	135	59.7	808	57.9	
Black	663	40.9	89	39.2	574	41.1	
Other	17	1.1	3	1.3	14	1.0	
Hispanic							0.497
Non-Hispanic	1596	98.3	222	97.8	1374	98.4	
Hispanic	12	0.7	3	1.3	9	0.6	
Unknown	15	1.0	2	0.9	13	0.9	
Marital Status							0.004*
Not married	827	51.0	97	42.7	730	52.3	
Married	531	32.7	96	42.3	435	31.2	
Unknown	265	16.3	34	15.0	230	16.6	
Insurance							<0.001*
State health plan	299	18.4	74	32.6	225	16.1	

Medicaid	1324	81.6	153	67.4	1171	83.9	
Patient Metropolitan Status							0.361
Non-metropolitan	400	24.7	50	22.0	350	25.1	
Metropolitan	1223	75.3	177	78.0	1046	74.9	
Provider State							0.035*
Out of state	487	30.0	82	36.1	405	29.0	
In state	1136	70.0	145	63.9	991	71.0	
Disease Characteristics							
AJCC Stage							0.210
IIIB	391	24.1	47	20.7	344	24.6	
IV	1232	75.9	180	79.3	1052	75.4	
Grade							0.357
Low	194	12.0	27	11.9	167	12.0	
High	463	28.5	56	24.7	407	29.2	
Unknown	966	59.5	144	63.4	822	58.9	
Histology							<0.001*

Adenocarcinoma	607	37.4	125	55.1	482	34.5	
Large cell	143	8.8	8	3.5	135	9.7	
Squamous	389	24.0	33	14.5	356	25.5	
Mixed or other NSCLC	484	29.8	61	26.9	423	30.3	
Primary Site							0.969
Main bronchus	96	5.9	12	5.3	84	6.0	
Lobe	1155	71.1	164	72.3	991	71.0	
Overlapping lesion	48	3.0	7	3.1	41	2.9	
Lung and bronchus, NOS	324	20.0	44	19.4	280	20.1	
Year of Diagnosis							0.753
Prior to 2010	1152	71.0	159	70.0	993	71.1	
2010 or later	471	29.0	68	30.0	403	28.9	
Molecular Testing							0.002*
No	1583	97.5	214	94.3	1369	98.1	
Yes	40	2.5	13	5.7	27	1.9	

Abbreviations: N, number; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; SD, standard deviation
*Significant at the $p \leq 0.05$ level.

Table 6.2. Univariable and multivariable logistic regression results for receiving erlotinib

	Univariable Logistic Regression			Multivariable Logistic Regression		
	Unadjusted OR	**95% CI**	**P-value**	**Adjusted OR**	**95% CI**	**P-value**
Patient/Physician Characteristics						
Age at Diagnosis (years)	0.97	0.96-0.99	0.001*	0.97	0.96-0.99	0.004*
Sex			0.010*			0.048*
Male	Reference			Reference		
Female	1.45	1.09-1.92		1.35	1.00-1.81	
Race			0.779			
White	Reference					
Black	0.93	0.70-1.24				
Other	1.28	0.36-4.52				
Hispanic			0.557			
Non-Hispanic	Reference					
Hispanic	2.06	0.55-7.68				

Unknown	0.95	0.21-4.25				
Marital Status			0.004*			
Not married	Reference					
Married	1.66	1.22-2.26				
Unknown	1.11	0.73-1.68				
Insurance			<0.001*			<0.001*
State health plan	Reference			Reference		
Medicaid	0.40	0.29-0.54		0.29	0.20-0.42	
Patient Metropolitan Status			0.324			
Non-metropolitan	0.84	0.60-1.18				
Metropolitan	Reference					
Provider State			0.031*			<0.001*
Out of state	1.38	1.03-1.86		2.03	1.43-2.89	
In state	Reference			Reference		
Disease Characteristics						
AJCC Stage			0.199			

IIIB	Reference					
IV	1.25	0.89-1.77				
Grade			0.359			
Low	Reference					
High	0.85	0.52-1.39				
Unknown	1.08	0.69-1.69				
Histology			<0.001*			<0.001*
Adenocarcinoma	Reference			Reference		
Large cell	0.23	0.11-0.48		0.28	0.13-0.60	
Squamous	0.36	0.24-0.54		0.44	0.29-0.68	
Mixed or other NSCLC	0.56	0.40-0.78		0.64	0.46-0.91	
Primary Site			0.964			
Main bronchus	0.86	0.46-1.62				
Lobe	Reference					
Overlapping lesion	1.03	0.46-2.34				
Lung and bronchus, NOS	0.95	0.66-1.36				

Year of Diagnosis			0.738			
Prior to 2010	Reference					
2010 or later	1.05	0.78-1.43				
Molecular			0.001*			0.018*
No	Reference			Reference		
Yes	3.08	1.57-6.06		2.37	1.16-4.85	

Abbreviations: CI, confidence interval; N, number; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OR, odds ratio
*Significant at the p≤0.05 level.

Table 6.3. Univariable and multivariable Cox proportional hazards regression for overall survival

	Univariable Cox Proportional Hazards Regression			**Multivariable Cox Proportional Hazards Regression**		
	Unadjusted HR	**95% CI**	**P-value**	**Adjusted HR**	**95% CI**	**P-value**
Patient/Physician Characteristics						
Age at Diagnosis (years)	1.01	1.01-1.02	<0.001*	1.01	1.00-1.01	0.007*
Sex			0.080			
Male	Reference					

Female	0.91	0.82-1.01				
Race			0.768			
White	Reference					
Black	0.96	0.87-1.07				
Other	0.97	0.59-1.59				
Hispanic			0.370			
Non-Hispanic	Reference					
Hispanic	0.67	0.35-1.28				
Unknown	1.21	0.71-2.05				
Marital Status			0.914			
Not married	Reference					
Married	0.98	0.87-1.10				
Unknown	1.01	0.87-1.16				
Insurance			0.547			
State health plan	Reference					
Medicaid	1.04	0.91-1.19				

Patient Metropolitan Status			0.902			
Non-metropolitan	0.99	0.88-1.12				
Metropolitan	Reference					
Provider State			<0.001*			<0.001*
Out of state	0.74	0.66-0.83		0.76	0.68-0.85	
In state	Reference			Reference		
Disease/Treatment Characteristics						
AJCC Stage			<0.001*			<0.001*
IIIB	Reference			Reference		
IV	1.82	1.60-2.06		1.96	1.73-2.23	
Grade			0.005*			
Low	Reference					
High	1.28	1.07-1.54				
Unknown	1.31	1.11-1.55				
Histology			0.074			
Adenocarcinoma	Reference					

Large cell	1.20	0.99-1.45				
Squamous	1.13	0.99-1.29				
Mixed or other NSCLC	1.15	1.02-1.31				
Primary Site			0.001*			0.010*
Main bronchus	1.19	0.96-1.48		1.20	0.97-1.49	
Lobe	Reference			Reference		
Overlapping lesion	1.38	1.02-1.85		1.37	1.02-1.82	
Lung and bronchus, NOS	1.25	1.10-1.42		1.18	1.04-1.35	
Year of Diagnosis			0.078			0.020*
Prior to 2010	Reference			Reference		
2010 or later	0.90	0.80-1.01		0.87	0.77-0.98	
Molecular			0.005*			0.024*
No	Reference			Reference		
Yes	0.59	0.41-0.85		0.65	0.45-0.95	
Erlotinib			<0.001*			<0.001*
No	Reference			Reference		

Yes	0.68	0.59-0.79		0.65	0.56-0.75	

Abbreviations: CI, confidence interval; HR, hazards ratio; N, number; NOS, not otherwise specified; NSCLC, non-small cell lung cancer

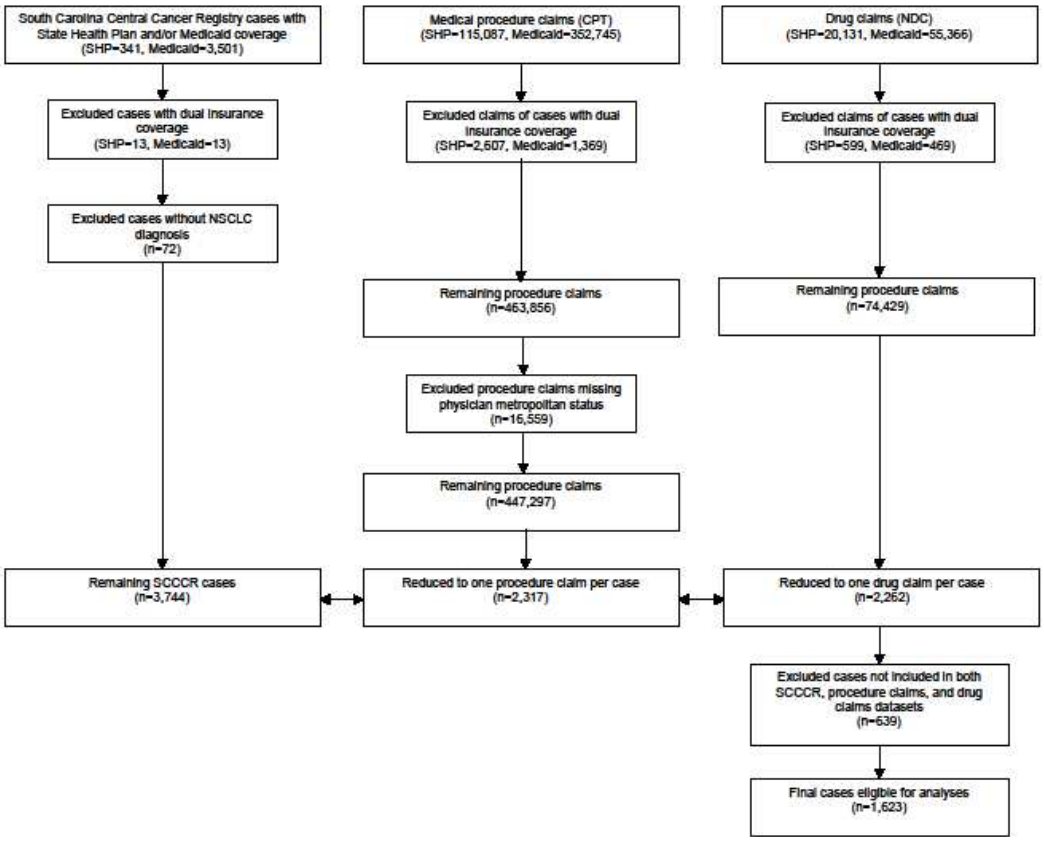
*Significant at the p≤0.05 level.

Table 6.4. Comparison of adjustment methods for estimating the impact of erlotinib utilization on overall survival

	Comparison of Adjusted Cox Proportional Hazards Regression Methods		
Method	**Adjusted HR**	**95% CI**	**P-value**
Cox PH model, individual covariates	0.65	0.56-0.75	<0.001*
Propensity score, parsimonious	0.57	0.46-0.71	<0.001*
Propensity score, non-parsimonious	0.59	0.48-0.73	<0.001*

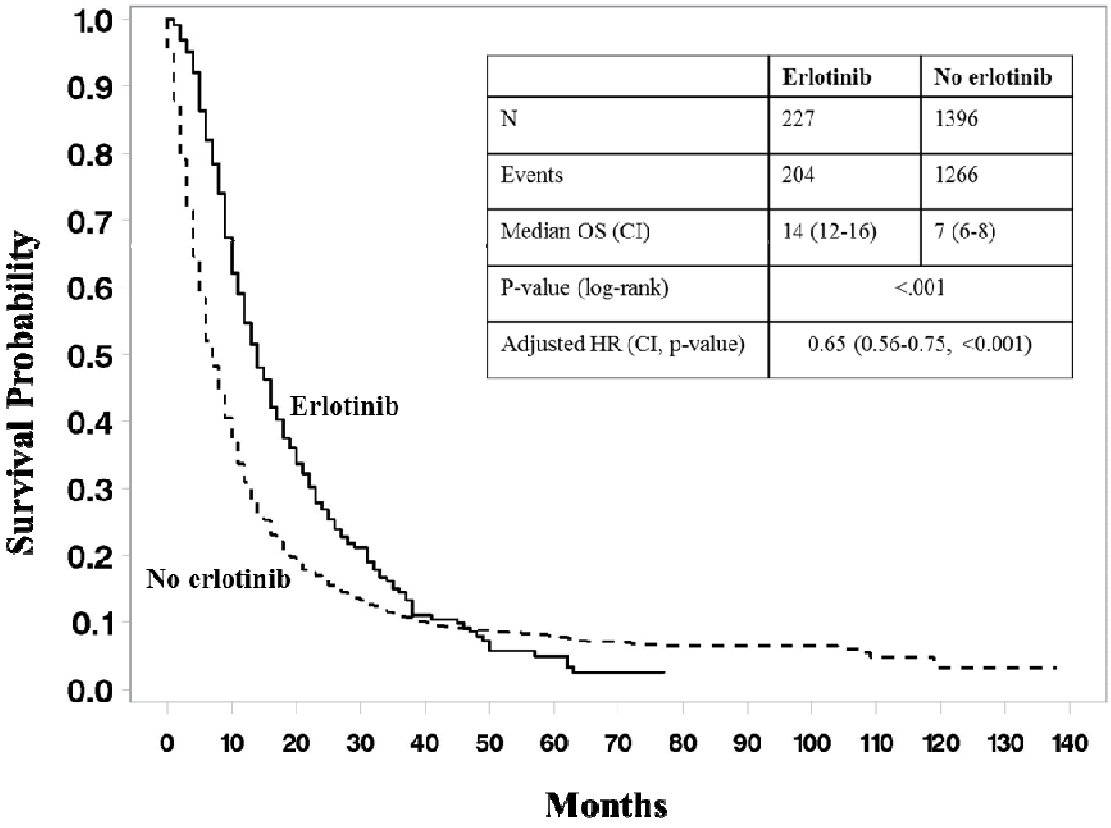
Abbreviations: CI, confidence interval; HR, hazards ratio; PH, proportional hazards

*Significant at the p≤0.05 level.



Abbreviations: NSCLC, non-small cell lung cancer; SCCCR, South Ca160rolina Central Cancer Registry; SHP, State Health Plan

Figure 6.1. Lung cancer registry case and corresponding claims inclusion and exclusion



	Erlotinib	No erlotinib
N	227	1396
Events	204	1266
Median OS (CI)	14 (12-16)	7 (6-8)
P-value (log-rank)	<.001	
Adjusted HR (CI, p-value)	0.65 (0.56-0.75, <0.001)	

Figure 6.2. Overall survival for all non-small cell lung cancer patients, stratified by whether they received (solid line) or did not receive (dashed line) erlotinib

CHAPTER VII:

SUMMARY

Conclusion

This dissertation focused on two approaches to improving outcomes for patients with lung cancer --- early diagnosis through screening with low-dose computed tomography and utilization of precision medicine. The latter included two topics of interest, molecular testing and targeted therapies, specifically administration of erlotinib.

Lung cancer screening with annual LDCT reduces all cause and lung cancer mortality and is recommended by leading public health agencies. However, national rates of LDCT utilization remain low and this impedes early diagnosis of lung cancer. Family physicians reported feeling responsible for lung cancer screening discussions and LDCT follow-up. While the majority of family physicians interviewed reported making at least one LDCT referral, they acknowledged that their knowledge of lung cancer screening is suboptimal. To ensure that patients are receiving the appropriate information regarding the risks and benefits of lung cancer screening and are engaged in the decision-making process, educational outreach initiatives highlighting the importance of lung cancer screening using LDCT in high risk patients, as well as the risks and benefits of LDCT, are warranted. Additionally, education outlining the process for making a LDCT referral and billing for both the lung cancer screening counseling visit and LDCT is encouraged. Tools to assist clinicians both at the point of care, such as decision aids and

copay estimators, and to make LDCT referrals (e.g., easy to use electronic order forms) are likely to increase utilization of lung cancer screening in the primary care setting.

Along with early detention, new precision medicine tools are available to help providers guide treatment decisions for patients with advanced lung cancer. Tumor molecular testing was low in South Carolina (~2%), as was erlotinib utilization (~14%), but patients who received these had a 7 month increase in survival over patients who did not receive molecular testing or erlotinib. Educational efforts should be targeted towards oncologists and oncology advanced care practioners and should focus on demonstrating the importance of molecular testing to provide the information needed to select the most appropriate treatment option. Additionally, institutional efforts to support oncologists, such as molecular tumor boards, care pathways, and electronically accessible order forms, should continue to be developed and implemented.

In a traditionally underserved disease area, we must continue to raise awareness of the ability of emerging technologies, such as LDCT and molecular testing, to support improved lung cancer outcomes. Additionally, we should advocate for insurance coverage of these services. We should also continue to provide information to providers and patients that these services are available and provide direction on how to access the services.

Future Research

Additional research in the areas of lung cancer screening and molecular testing are needed and this dissertation identified specific areas to target. Utilization rates for both LDCT and molecular testing are low in South Carolina and nationally and reasons

for this should be further explored. Additionally, utilization of molecular testing in other cancer sites (e.g., colorectal) could be explored.

With regards to lung cancer screening, areas of further research interest include identifying how family physician practices follow up with their patients after a referral for a LDCT and determining the best approaches to documenting and billing for lung cancer screening counseling visits. Additionally, future research could assess the perspectives and practices of non-physician providers (e.g. nurse practioners, physician assistants), who are also able to engage in shared decision-making discussions with high risk patients and provide referrals for lung cancer screening.

Future research into precision medicine utilization in lung cancer should also consider use of datasets that include patient level (e.g., smoking history, molecular test results) and provider level variables (e.g., geographic location) that we were not able to include in our analyses of molecular testing and erlotinib utilization. Now that new CPT codes are available that provide additional detail on the specific genes tested, we encourage additional research in this area using these codes in national datasets, such as SEER-Medicare.

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APPENDIX A

FAMILY PHYSICIAN SURVEY ON LOW-DOSE CT LUNG CANCER SCREENING

The **Carolina Physicians' Lung Cancer Screening Survey** is a survey of family physicians in North and South Carolina. In this survey, we request that you answer questions about your attitudes and practices related to lung cancer screening procedures, **even if you are not currently recommending screening to your patients.** This topic has relevance for clinicians and health care researchers because lung cancer is the most common cause of cancer-related death in the U.S. and our state.

All information you provide in this survey will remain confidential. Participation is voluntary; however, we would greatly appreciate your participation since not responding could affect the accuracy of our results, and your point of view may not be adequately represented in the survey findings. We request you fill out the survey within one week of receiving our invitation via email. You cannot save the survey and return to it later; it must be completed in one session. All your information will be kept confidential and results will only be reported in aggregate form. Your name will not be connected with any information you provide.

If you have any questions, please call the study Principal Investigator Dr. Jan Eberth at 803-576-5770 or at jmeberth@mailbox.sc.edu. You can also contact Dr. Scott Strayer, a fellow family practitioner, at Scott.Strayer@uscmed.sc.edu or Dr. Edward Kim, a thoracic oncologist, at Edward.Kim@carolinashealthcare.org.

By proceeding to the survey/questionnaire on the next page you are indicating that you have read and understood this consent form and agree to participate in this research study.

Thank you for your participation!

Practice Setting and Demographics

1. **Please select your practice setting:**
   [ ] Hospital
   [ ] Private practice
   [ ] Group practice
   [ ] Health Maintenance Organization
   [ ] Community health center
   [ ] Medical school/university
   [ ] Other; please specify:
   _____

2. **In which state and county do you practice?**

State	
County	

3. **Please select your gender:**
   [ ] Male
   [ ] Female

4. **Please select your race (Check all that apply)**
   [ ] White
   [ ] Black or African American
   [ ] American Indian or Alaska Native
   [ ] Asian
   [ ] Hawaiian/Pacific Islander
   [ ] Other

   4a. Do you consider yourself Hispanic/Latino?
   [ ] Yes
   [ ] No

5. **Please select your age range:**
   [ ] 20-29 [ ] 60-69
   [ ] 30-39 [ ] 70-79

[ ] 40-49 [ ] 80+
[ ] 50-59

6. **What is your specialty?**
   [ ] Family medicine
   [ ] General medicine
   [ ] Internal medicine
   [ ] Other, please specify:

LDCT Screening Recommendations & Guidelines

7. **Which, if any, lung cancer screening test would you recommend for the following patients? Assume that these patients have:**
   - No symptoms of lung cancer
   - Never been screened for lung cancer before
   - Expressed no interest for lung cancer screening
   - Have no occupational exposure to lung carcinogens

	No screening	Chest x-ray	Low-dose CT
50-year-old nonsmoker with: • 30 years second-hand smoke exposure from spouse			
50 year old current smoker with: • 20 pack-years of smoking • Family history of lung cancer			
60 year old current smoker with: • 30-year pack history			
70 year old former smoker with: • 30-year pack history • Quit smoking 20 years ago			

8. **How often should patients at high risk for lung cancer be screened using low-dose CT (assuming low-dose CT is performed solely for lung cancer screening)?**
   [ ] Every 6 months
   [ ] Every year
   [ ] Every 2 years
   [ ] Every 3 years

9. **To the best of your knowledge, do the following organizations recommend the use of low-dose CT for lung cancer screening in asymptomatic, high risk patients? Check one box in each row.**

	Yes, recommend	No, don't recommend	Not sure
U.S. Preventive Services Task Force			
American Cancer Society			
National Comprehensive Cancer Network			
American College of Radiology			
American Academy of Family Physicians			

10. I have the time I need to stay abreast about current cancer screening guidelines.
[ ] Agree [ ] Disagree

Benefits and Risks of Screening

11. What do you consider to be the benefits of low-dose CT (for lung cancer screening) for patients at high risk for lung cancer? Check all that apply.
[ ] Reduces lung cancer mortality
[ ] Increases the chances of finding lung cancer at an earlier stage
[ ] Low rate of false positives
[ ] It is beneficial for all patients, regardless of smoking history
[ ] No benefits

12. What do you consider to be the risks of low-dose CT for lung cancer screening for patients at high risk for lung cancer? (Check all that apply)
[ ] Positive screening results rarely result in a lung cancer diagnosis
[ ] High rate of false negatives, leading to inaccurate reassurance given to people with lung cancer
[ ] Psychological stress or anxiety for the patient
[ ] May lead to unnecessary diagnostic procedures
[ ] Exposure to radiation increasing cancer risk
[ ] No risks

Cost of Screening

13. Do Medicare/Medicaid cover the cost of low-dose CT for lung cancer screening for high risk patients?
[ ] Yes
[ ] No
[ ] Not Sure

14. Do most private insurers cover the cost of low-dose CT for lung cancer screening for high risk patients?

[ ] Yes
[ ] No
[ ] Not sure

Practice Patterns

15. During the past year did any of your patients ask if they can or should be screened for lung cancer?

[ ] Yes ⟶ About how many patien ☐
[ ] No

16. How many patients have you referred for low-dose CT (for lung cancer screening) in the <u>past month</u>? (Give your best estimate)

☐

17. How many patients have you referred for low-dose CT (for lung cancer screening) in the <u>past year</u>? (Give your best estimate)

☐

18. Medicare/Medicaid require that patients considering LDCT screening for lung cancer first have a shared decision-making visit with a healthcare provider. A shared decision-making visit should include a discussion of the benefits and harms of LDCT screening, follow-up diagnostic testing, over-diagnosis, the false positive rate and total radiation exposure.

To what extent do you feel comfortable engaging in a discussion of this nature with your patient?
[ ] I was not aware of this requirement
[ ] Very comfortable
[ ] Somewhat comfortable
[ ] Somewhat uncomfortable
[ ] Very uncomfortable
[ ] Unsure

19. Medicare/Medicaid require that providers counsel their patients on smoking cessation, or encourage them to remain abstinent from smoking if former smokers, before referring them for lung cancer screening.
To what extent do you feel comfortable engaging in a smoking cessation/abstinence discussion with your patient?
[ ] I was not aware of this requirement

[ ] Very comfortable
[ ] Somewhat comfortable
[ ] Somewhat uncomfortable
[ ] Very uncomfortable
[ ] Unsure

20. How likely would you be to engage in this shared decision-making and smoking cessation discussion with your patient if the visit took:

	Very likely	Likely	Not likely	Not very likely
< 5 minutes				
5-10 minutes				
>10 minutes				

21. How often to you discuss the risks and benefits of low-dose CT with patients you recommend for lung cancer screening?

Always	Frequently	Sometimes	Infrequently	Never

22. Which best describes your practice style concerning low-dose CT for lung cancer screening? (Please check only one box.).

Recommend screening to patients without discussion of risks and benefits	
Discuss risks and benefits, then recommend screening	
Discuss risks and benefits, then let patient decide to be screened	
Discuss risks and benefits, then recommend against screening	
Do not discuss risks and benefits or recommend screening	
Recommend against screening	

23. If a patient recommended for low-dose CT initially declines screening, I still encourage him/her to participate in the screening procedure.

[ ] Agree [ ] Disagree

Attitudes towards Screening

24. Tell us about your opinions about low-dose CT for lung cancer screening. Check one box per row.

	Strongly Agree → Strongly Disagree				
	1	2	3	4	5
The benefits of low-dose CT outweigh the risk for patients at high risk for lung cancer.					
There is clear evidence that low-dose CT for lung cancer screening saves lives.					
Low-dose CT screening for lung cancer is cost-effective.					
The rate of false positives for low-dose CT is too high.					
Low-dose CT creates enough anxiety to negate the value of screening.					
The scientific evidence is strong enough to warrant a screening guideline for high risk patients.					
There is no need to educate patients about low-dose CT because in general they want to be screened.					
If cost were not an issue, I would recommend low-dose CT screening to my patients at high risk for lung cancer.					
I am not sure how to refer my patients for LDCT screening.					

Management of LDCT Screening Results

25. If a patient is found to have a positive low-dose CT scan for lung cancer, to what extent would you be comfortable managing the follow-up of your patient?

[ ] Very comfortable
[ ] Somewhat comfortable
[ ] Somewhat uncomfortable
[ ] Very uncomfortable
[ ] Unsure

Future Contact

26. Are you interested in being contacted at a later date to provide further information on your opinions regarding lung cancer screening?

[ ] Yes [ ] No

26a. If you answered yes to Question 26, please provide contact information that you would like us to use to reach you in follow-up studies (name, address, phone and email). Note that we will use this information solely to contact you for gathering data in future studies, and we will not share your name or contact information with any third parties or outside groups. Your name and contact information will be stored securely by our study group.

APPENDIX B

FAMILY PHYSICIAN INTERVIEW GUIDE

Introduction to physician via email (Initial contact attempt):

Greetings Dr. [INSERT NAME],

Last year, you participated in a survey on lung cancer screening through the [Carolinas HealthCare System/South Carolina Academy of Family Physicians] and agreed to be contacted to assist us with future research on lung cancer screening. If you recall, you completed this survey [VIA AN ELECTRONIC SURVEY LINK/ON PAPER-SENT BY CAROLINAS HEALTHCARE SYSTEM/SC ACADEMY OF FAMILY PHYSICIANS-AT THE ANNUAL MEETING].

I am a graduate student working with University of South Carolina (USC), Medical University of South Carolina (MUSC), and Levine Cancer Institute (LCI) researchers, Jan Eberth, Scott Strayer, Kathleen Cartmell, and Edward Kim, to conduct a research project on physician's perceptions of low-dose CT screening for lung cancer and we would like to hear more about your thoughts on this topic. It's important that we learn what physicians know and how they feel about screening patients for lung cancer using low-dose CT, since there are inherent risks and benefits.

We realize that your time is valuable, and we are willing to provide an incentive for participation in a telephone interview. We anticipate that the interview will take approximately 30-45 minutes. Are you willing to participate in the telephone interview? If so, please respond to this email with your preferred date/time of the interview. If you do not wish to participate, please let us know and we will note this.

Thank you for your time and we look forward to hearing from you!

Jennifer L. Ersek, MSPH, PhD(c)
(704) 654-0884
ersek@email.sc.edu
Dr. Jan M. Eberth (USC)
Dr. Kathleen Cartmell (MUSC)
Dr. Scott Strayer (USC)
Dr. Edward Kim (LCI)

Introduction to physician via email (Follow-up contact attempt):

Greetings Dr. [INSERT NAME],

We are following up to see if you received our email sent to you on [DATE]. If you recall, you participated in a survey on lung cancer screening through the [Carolinas HealthCare System/South Carolina Academy of Family Physicians] and agreed to being contacted to assist us with future research on lung cancer screening. You completed this initial survey [VIA AN ELECTRONIC SURVEY LINK/ON PAPER-SENT BY CAROLINAS HEALTHCARE SYSTEM/SC ACADEMY OF FAMILY PHYSICIANS-AT THE ANNUAL MEETING].

Please let us know if you are willing to participate in our telephone interview. For your valued time, we will provide a gift card to you. If you agree, please respond to this email with potential dates/times for the interview.

If you do not wish to participate, please also let us know and we will remove you from our contact list.

Thank you again for your time. We look forward to hearing from you soon!

Jennifer L. Ersek, MSPH, PhD(c)
(704) 654-0884
ersek@email.sc.edu
Dr. Jan M. Eberth (USC)
Dr. Kathleen Cartmell (MUSC)
Dr. Scott Strayer (USC)
Dr. Edward Kim (LCI)

Reminder email to physician 1-3 days prior to scheduled interview:

Greetings Dr. [INSERT NAME],

I am looking forward to speaking with you soon about your thoughts on using low-dose computed tomography for lung cancer screening. I just wanted to remind you that our interview is scheduled for [Date/Time]. I will call you at [Phone number] / please call me at (803) 580-5156.

Please let me know if you have any questions.

Thank you again for your time,

Jennifer L. Ersek, MSPH, PhD(c)

Introduction to receptionist answering phone (Final contact attempt or any attempt for physicians who did not provide a valid email):

Hello, my name is Jennifer Ersek and I am calling from the University of South Carolina. Last year, Dr. [INSERT NAME] participated in a survey on lung cancer screening through the [Carolinas HealthCare System/South Carolina Academy of Family Physicians] and agreed to being contacted for a phone interview. What is the best way to schedule a few minutes with Dr. [INSERT NAME] to discuss this phone interview?

Email/phone [EMAIL: Ask for email address.] Is he/she available to speak or could I schedule another time to talk with Dr. [INSERT NAME] to discuss this interview?

Introduction to physician via phone:

Hi Dr. [INSERT NAME], my name is Jennifer Ersek and I am a graduate student at the USC. We are contacting you today because you indicated interest in assisting us with future research on lung cancer screening when you participated in our survey through the Carolinas HealthCare System/SC Academy of Family Physicians last year. If you recall, you either completed this survey [ELECTRONICALLY THIS YEAR OR IN PAPER FORMAT AT THE SC ACADEMY OF FAMILY PHYSICIANS ANNUAL MEETING/VIA EMAIL SURVEY LINKLAST YEAR].

I am working with University of South Carolina and MUSC researchers to conduct a research project on physician's perceptions of low-dose CT screening for lung cancer and we would like to hear more about your thoughts on this topic. It's important that we learn what physicians know and how they feel about screening patients for lung cancer using low-dose CT, since there are inherent risks and benefits.

We realize that your time is valuable, and we are willing to provide *AN INCENTIVE* for participation in the interview. We anticipate that the interview will take approximately 30-45 minutes. Are you willing to participate in the telephone interview? We can schedule a more convenient time for you if you prefer or we can even do the interview now.

If yes: Great! We are looking forward to learning about your thoughts and any experience you may have with lung cancer screening in your practice.

If no: Thank you very much; I hope you have a pleasant day.

***Consent*:** Let me quickly review a few specifics about this study before we continue.

Dr. Jan Eberth, a professor at the University of South Carolina, and her research team are asking you to participate in this interview research study to learn more about your thoughts and use of lung cancer screening. You are being asked to take part because you are a family practice physician member of the South Carolina Chapter of the American Academy of Family Physicians or an employee at the Carolinas HealthCare System and you provided your contact information to us for future research.

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, your decision to not participate will not in any way harm your relationship with the University of South Carolina or the study investigator. You are free to stop being in the study if you change your mind after starting the interview. As mentioned previously, for participation in this study, you will receive *AN INCENTIVE*.

In this study, your interview responses (i.e., your study record) will be recorded. We will then transcribe your recorded interview. We will not use your real name or any other

identifying information in any manuscript or publication of any sort. The risks of participation in this study are minimal but include the chance of study records being compromised. However, the records of this study will be kept private to the best of our ability. Your name and the name of your practice will not be associated directly with any of the statements you make during the interview. The data generated from this study (i.e. recorded interviews and transcripts) will be kept in a secure location. Benefits of this study include the potential to better understand how physician's view and utilize lung cancer screening in South Carolina.

If you have any questions regarding the study, I will be happy to answer them today, or via email in the future. The email address of the Principal Investigator of this study is jmeberth@mailbox.sc.edu. If you have any questions regarding your rights as a study participant, please feel free to contact the University of South Carolina Institutional Review Board (IRB) by calling Lisa Marie Johnson, IRB Manager, Office of Research Compliance, University of South Carolina at (803) 777-7095 or emailing her at LisaJ@mailbox.sc.edu. Do you need me to repeat that phone number or email address? If there are no questions, do I have your consent to proceed with the survey?

If yes: Great! We don't expect you to know all of the answers to all of the questions we have for you today. If you don't know how to respond, please just let us know that.

If no: Thank you so much for your time today. We appreciate you taking the time out of your busy day to take our phone call. Have a great day.

Interview Questions:

1. About Your Practice

1.1. How many physicians and advanced practioners, such as physician assistants or nurse practioners, are in your practice? Do most practice full time?
1.2. Does your practice accept Medicare/Medicaid? What proportion of your patients are covered by Medicare/Medicaid?
1.3. What can you tell me about the patients you see in your practice? Do you see many cancer/lung cancer patients? Have you ever had any patients diagnosed with lung cancer? If so, what can you tell me about them?

2. Current Evidence and Guidelines for LDCT Screening for Lung Cancer

First, we'd like to talk about current evidence and guidelines for lung cancer screening with low-dose computed tomography.

2.1. How do you find out about new guidelines?
2.2. What can you tell me about the current lung cancer screening guidelines? What is recommended? [Probe: If they don't specifically mention the organizations that make these recommendations ask, 'What organization specifically recommends the strategy you refer to?']

2.3. What can you tell me about the type of person who should be recommended for lung cancer screening? [Probe: Is screening recommended for everyone? Former smokers?]
2.4. What can you tell me about the scientific evidence surrounding LDCT screening for lung cancer? [Probe: Have you heard about the National Lung Screening Trial or the Prostate Lung Colon Ovarian Cancer Screening Trial? If yes: What have you heard? If no: PLCO-no mortality benefit with chest x-ray; NLST-20% reduction in mortality with LDCT.]

3. Who to Talk to About Lung Cancer Screening in the Clinic

Next, let's talk about who you talk to about lung cancer screening.

3.1. How do you make the decision on who to talk to about lung cancer screening? [Probe: What types of patients would you discuss lung cancer screening with? Do you have a way to systematically identify candidates for screening?]
3.2. What (if any) types of patients in your clinic ask on their own to be screened for lung cancer or ask for your opinion about screening?
3.3. Patients considered to be high risk for lung cancer by the National Comprehensive Cancer Network (Category B) are defined as those ages 55 to 80 years, asymptomatic, 30 pack year smoking history, current or have quit in past 15 years.]
How would you manage a patient who is not considered to be high risk, but is requesting a referral for low-dose computed tomography screening? Are there any circumstances where you would NOT recommend LCDT to someone who may fit the definition of high risk?

4. Discussing LDCT in the Clinic

The goal of the next set of questions is to learn more about how you and your colleagues recommend (or do not recommend) LDCT to patients in your offices, clinics.

4.1. To what extent do you think other healthcare providers in your region are recommending LDCT?
4.2. What is your experience with recommending or not recommending LDCT screening for high risk patients? [Probe: If they never use LDCT screening, why not and do they intend to in the future? Can you describe the process for how you discuss lung cancer screening with your patients? [Probe: Does this process include shared decision making? Shared decision making is typically defined as a 'collaborative process that allows patients and their providers to make health care decisions together". SDM considers the best scientific evidence available, as well as the patient's values and preferences. Probe: Did you know that you can bill for the shared-decision making visit? Describe how this communication-oriented visited that can be billed for Medicare beneficiaries and that the purpose is for the patient and physician to discuss risks/benefits of screening, etc.] How

comfortable are you with conducting a shared decision-making visit for lung cancer screening with your patients, given the various pros and cons?

4.3. What are your thoughts on taking time during the patient's appointment to discuss lung cancer screening when the patient's original purpose was a sick visit or annual checkup?

4.3.1. How much time (if any) could you dedicate to this discussion? Would you request the patient schedule a new appointment to talk specifically about lung cancer screening?

4.4. How would you approach LDCT screening among patients who lack insurance? [Probe: How would you discuss the costs of follow-up care and treatment if lung cancer is found during screening?]

4.5. Do you feel that integrating lung cancer screening visit is feasible in your clinic? If yes, what are some facilitators? If no, what are some barriers to integration?

5. **Making the Low-Dose Computed Tomography Referral and Following Up**

Next, let's talk about making the LDCT referral and subsequent follow-up with the patient.

5.1. How do you feel about the role primary care providers have in regard to lung cancer screening?

5.1.1. Would you prefer to refer patients directly to a pulmonologist or radiologist for the shared decision-making visit OR would you prefer to do it yourself?

5.2. Have you ever referred anyone for LDCT screening? If yes, continue to 5.3. If no, do you intend to do so in the future? What are the reasons why you would not refer anyone? (Probe: Administrative reason, complexity with billing, etc)

5.3. For patients you have referred, did you have any difficulty making the LDCT referral? [Probe: not know where to refer them, what to document on the referral paperwork, etc…] Did you have any difficulty getting the scan reports?

5.4. What is the process for following-up with a patient with a positive lung nodule? [Probe: What type of follow up would you recommend for a patient with a pulmonary nodule? Is there a pulmonary nodule clinic in your area? Who do you think should review the results with the patient?]

7/7/16 ADDITIONAL QUESTION--For physicians who do not appear to be supportive of lung cancer screening with LDCT: What would kind of information or evidence would be needed to gain your support for LDCT screening?

Conclusion:

Well, I think that about covers the questions we had for you today. Is there anything else you would like to add or discuss? Do you have any questions for us?

In the next few days, I will also be emailing you a document containing additional information and resources for you about low-dose computed tomography screening.

One last thing, we think we will have enough physicians participating in these qualitative interviews, however, in case some physicians change their mind about participating, do you know of any other physicians that might like to participate? [If so, ask if they prefer to reach out to the physician with our contact information or if they would like to provide us with the physician's contact information that is fine also.]

Thank you again, so much, for the time you spent with us today. Please feel free to contact us if you have any questions about the study or lung cancer screening. We will try to help you in any way!

APPENDIX C

COMMON PROCEDURE TERMINOLOGY

BILLING CODES FOR MOLECULAR TESTING

Code	Short Description	Long Description
83890	MOLECULE ISOLATE	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	MOLECULE ISOLATE NUCLEIC	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	MOLECULAR DIAGNOSTICS	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83893	MOLECULE DOT/SLOT/BLOT	Molecular diagnostics; dot/slot blot production, each nucleic acid preparation
83894	MOLECULE GEL ELECTROPHOR	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	MOLECULAR DIAGNOSTICS	Molecular diagnostics; nucleic acid probe, each
83897	MOLECULE NUCLEIC TRANSFER	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation
83898	MOLECULE NUCLEIC AMPLI EACH	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	MOLECULE NUCLEIC AMPLI 2 SEQ	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	MOLECULE NUCLEIC AMPLI ADDON	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure). Used in conjunction with 83900
83902	MOLECULAR DIAGNOSTICS	Molecular diagnostics; reverse transcription

83903	MOLECULE MUTATION SCAN	Molecular diagnostics; mutation scanning, by physical properties (eg, single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'ase A), single segment, each
83904	MOLECULE MUTATION IDENTIFY	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83905	MOLECULE MUTATION IDENTIFY	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83906	MOLECULE MUTATION IDENTIFY	Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment
83907	LYSE CELLS FOR NUCLEIC EXT	Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen
83908	NUCLEIC ACID SIGNAL AMPLI	Molecular diagnostics; amplification, signal, each nucleic acid sequence
83909	NUCLEIC ACID HIGH RESOLUTE	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	GENETIC EXAMINATION	Molecular diagnostics; interpretation and report
83913	MOLECULAR RNA STABILIZATION	Molecular diagnostics; RNA stabilization
83914	MUTATION IDENT OLA/SBCE/ASPE	Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE])
88384	EVAL MOLECULAR PROBES 11-50	Array-based evaluation of multiple molecular probes; 11 through 50 probes
88385	EVAL MOLECUL PROBES 51-250	Array-based evaluation of multiple molecular probes; 51 through 250 probes
88386	EVAL MOLECUL PROBES 251-500	Array-based evaluation of multiple molecular probes; 251 through 500 probes