STRATEGIES FOR INCREASING EGFR MUTATION TESTING OF PATIENTS WITH NON-SMALL CELL LUNG CANCER

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Public Health in the Department of Health Policy and Management in the Gillings School of Global Public Health.

Chapel Hill
2014

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ABSTRACT

Patricia Pozella: Strategies for Increasing EGFR Mutation Testing of Patients with Non-Small Cell Lung Cancer
(Under the direction of Edward Brooks and Suzanne Hobbs)

Background: More than 228,000 people are diagnosed with non-small cell lung cancer (NSCLC) each year in the United States, and most die within a year. Newer targeted medications, including erlotinib and afatinib, work at a molecular level to produce profound and sustained benefit for a small percentage of patients. Specific genetic mutations, including changes in the EGFR gene, identify individuals more likely to respond to targeted therapies. Published literature shows that using results of EGFR testing to guide treatment decisions results in significantly better treatment outcomes. Mutation testing is done routinely at most academic medical centers and cancer centers; however, use in community settings is highly variable and significantly less common. Reasons for the disparity in testing rates are unknown.

Methods: Twenty-three key informant interviews were conducted with community oncologists practicing in southeastern states to identify facilitators and barriers to use of EGFR testing in community settings.

Results: Two characteristics predicted an increased likelihood of EGFR testing of patients with advanced or metastatic NSCLC, including less time passed since completion of oncology training, and treating a higher number of patients with NSCLC each month. The most frequently mentioned facilitator was clinical literature and treatment guidelines. The most commonly cited barriers to testing included patient-related reasons, such as patient health and unwillingness to be tested, and oncologist-specific reasons. Eight-seven percent of oncologists who reported testing some

or none of their patients expressed confidence in their abilities to make optimal treatment decisions based on clinical judgment and experience instead of relying on test results.

Conclusions: This study suggests there is much work to be done to increase use of EGFR testing by oncologists practicing in community settings. The first step involves convening a task force with representatives from a variety of constituencies that will develop and implement an integrated communications plan focusing on three audiences--community oncologists, other healthcare professionals, and patients, families, caregivers, and advocates located in North Carolina. Each tactic will be measured and evaluated after completion based on pre-established objectives. Regional and national expansion of the communications plan will be based on the results of the North Carolina pilot.

To my father, William (Bill) Pozella, who encouraged me to the very end and gave me the inspiration to finish. I know he would be proud.

I miss him every day and will always love him.

ACKNOWLEDGMENTS

This has been a very long journey but I had tremendous support from many people, who provided much needed encouragement, understanding and nudging when I needed it most. I know my friends and family share in the joy (and relief) that comes from my finishing this milestone. They never lost faith and confidence in my ability to cross the finish line. I am very thankful to have had them along for the ride. I want to say special thanks to the following:

To my family and friends

My wonderful daughter, Cailyn. You have been with me every step of the way, as always. I am blessed to have you in my life. You have provided inspiration and encouragement, and have spent countless hours doing what was needed so that I could finish this dissertation. I am very proud of you and your accomplishments. As with so many things in our lives, we share the momentous achievement of graduating at the same time (but, as promised, I crossed the finish line first). Love you, always.

My Mom for loving me.

My Uncle Joe (DiPace) – you took over from my Dad when the time came. You gently nudged me along the path. Your encouragement helped keep me going.

My friends Beth, Thanta, and Mary Anne – you encouraged me and have been there when I needed you most.

My friend Donna – you cleared the runway and did more than your share to give me the time I needed to write. I am grateful for all you do for me.

To my committee

Ned Brooks – My wonderful committee chair and the most patient person I know. I am so fortunate you played this important role in my life and education. You have been there for me and have never lost faith that I would graduate (eventually). I am grateful for your kindness, guidance, and wisdom. Thank you for hanging in there until I finished!

Sue Hobbs – You, too, have had patience and have provided critical guidance and support. Being the last holdover from the residential program has led to some bumps in the road; you have eliminated roadblocks that would have kept me from completing my degree. Thank you for co-chairing with Ned. I cannot not imagine having two better people guiding my way.

Beth Balkite, John Paul and Stephanie Wheeler – Thank you for being on my committee and for providing valuable guidance, feedback, and support.

Others Important Carolinians

Lynette Jones – What would I have done without you? Thank you for all of your help navigating the bureaucracy.

Margaret Dardess – My mentor at GSK. I would not have begun this journey if you had not encouraged me to pursue a doctorate in public health. I have become a public health advocate, which contributes to my work on behalf of others. Thank you for having the insight to guide me in this direction.

Special Advisors

Special thanks to Jared Weiss, Amy Cipau, and Jennifer Garst – you have and will continue to play instrumental roles in the dissemination of these research findings and implementation of the plan outlined in chapter 5.

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CHAPTER 1

Overview

Prevention and treatment of lung cancer are major public health issues. Over 228,000 people are diagnosed in the U.S. with non-small cell lung cancer (NSCLC) each year; most are diagnosed with late stage incurable cancer and will die within one year (American Cancer Society, 2013). Beyond the cost in human lives, lung cancer treatments account for almost 10% of the billions spent each year on cancer care (ASCO, 2012; Mariotto, 2011) with most of the money being spent during patients' last year of life.

There are two main treatment options for these individuals—traditional chemotherapy and newer targeted oral medications. There are obvious advantages to taking an oral medication instead of receiving intravenous infusions; however, response rates to oral therapies used in a general population of patients being treated for advanced or metastatic NSCLC are very low (Shepard F. A., 2005). Researchers have discovered the presence of specific mutations in the epidermal growth factor receptor (EGFR) gene in a tumor sample predict treatment response to certain oral medications (Eberhard, 2008; John, 2009; Levenson, 2008; Maemondo, 2010; Mok, 2009; Riely, 2006). Molecular tests used to identify the presence of EGFR mutations are widely available and moderately priced (Printz, 2010).

For individuals who have an EGFR mutation, the response to an oral therapy can be dramatic and prolonged; however, these same people tend to do poorly when treated with traditional chemotherapy (Gandara, 2010; Gridelli, 2008; Lennes, 2011; Printz, 2010). The opposite is true for patients without an EGFR mutation. Selecting the wrong treatment approach has significant consequences in terms of morbidity, mortality, and cost.

The only way to know for sure if a patient's tumor harbors the EGFR mutation is to test for it (Cataldo, 2011; Gazdar A. , 2010; Lennes, 2011; Maione, 2010; Printz, 2010; Shepard F. A., 2011; West J. H., 2010). Despite overwhelming evidence that pretreatment EGFR testing is the best way to determine the most appropriate treatment option for individual patients with NSCLC, many oncologists do not test patients' tumors for EGFR mutations before prescribing treatment (Alt, 2011). Little is known about why. Lung cancer experts often speculate about the reasons, but there are no published data confirming their suspicions.

This research effort seeks to enhance the understanding of the factors oncologists consider when deciding whether to test tumor samples for EGFR mutations before prescribing treatment for patients with advanced or metastatic NSCLC. The research findings, along with insights gained from a review of relevant literature will be used to develop a plan for increasing the use of EGFR testing by oncologists.

Background

Cancer is a significant public health burden from both the prevention and treatment perspectives; over 1.6 million Americans are expected to be diagnosed with some form of cancer in 2013 (American Cancer Society, 2013). It is the second leading cause of death in the United States, behind cardiovascular disease, accounting for slightly more than one in four deaths annually (American Cancer Society, 2013; Janne, 2006; Jemal, 2010). Each year over 228,000, individuals in the U.S. receive the devastating news they have lung cancer.

More than 160,000 individuals succumb to lung cancer each year, making it the leading cause of cancer deaths in the U.S. Approximately 85% of people diagnosed with lung cancer die within five years of diagnosis primarily due to being diagnosed at an advanced stage (IIIB and IV) when the cancer is no longer localized to a single area and is incurable (Altecruse, 2010; American Cancer Society, 2013; Maione, 2010). Individuals diagnosed at an advanced stage usually have a very short

lifespan (Gazdar A. F., 2009; Perez-Soler, 2009; West, 2010). Median survival is 8 to 10 months at diagnosis even with aggressive treatment (American Cancer Society, 2013; Dancey, 2007; Levenson, 2008; Sequist L. B., 2007). The median time to cancer progression averages three to five months after initial treatment (Shepard F. A., 2005; Shepard F. A., 2005), and only 30 to 40% of patients are alive one year after diagnosis (Dowell, 2005).

The good news is there has been a great deal of progress made in recent years in the understanding of the underlying genetics of lung cancer (Amler, 2005; John, 2009; Murdoch, 2008; Printz, 2010; Sequist L. V., 2008), which has lead to the development of a small number of targeted drug therapies that prolong survival in a subset of patients diagnosed with advanced or metastatic NSCLC. In November 2004, the US Food and Drug Administration (FDA) approved one of the targeted medications, erlotinib (brand name Tarceva®), for use in patients with advanced NSCLC whose cancer has continued to progress after at least one prior traditional chemotherapy regimen (Genentech Inc., 2012; Huff, 2010).

As is the case with most new cancer therapies, the approval of erlotinib was trumpeted by media outlets, which generated significant enthusiam and interest among patients and the medical community (Arp, 2005; Beil, 2009; Calfee, 2006; Langreth, 2010; Pho, 2011; Tsao A. , 2001). Lester Crawford, MD, the acting FDA Commissioner was quoted in press coverage as saying, "'with the approval of Tarceva, thousands of patients with lung cancer will not only have access to another treatment option, but one that extends life'" (U.S. Food and Drug Administration, 2004). Indeed, a small percent of patients with advanced NSCLC have a dramatic and prolonged response to erlotinib (Shepard F. A., 2005; Shepard F. A., 2005); unfortunately, the vast majority of patients do not benefit from the medication, although media reports may suggest otherwise (Arp, 2005; Beil, 2009; Calfee, 2006; Langreth, 2010; Pho, 2011; Tsao A. , 2001).

The FDA approval of erlotinib was based on a single randomized, double-blind, placebo controlled study involving 731 patients (U.S. Food and Drug Administration, 2004). The response

rate in the group treated with erlotinib was 8.9% compared with less than 1% in the group treated with placebo. Overall survival for patients treated with erlotinib was two months longer than those treated with placebo (6.7 months vs. 4.7 months respectively), which is a statistically significant difference.

Clearly, the medication does not work for all patients, so clinicians are left with the task of attempting to prospectively identify individuals who are likely to be among the small percentage of people who will respond to the medication. Researchers have observed in clinical trials of erlotinib and a similar drug, gefitinib (brand name Iressa™), used in a general population of people with advanced or metastatic NSCLC that individuals who responded to medication tended to share certain easily identifiable characteristics (Giaccone G. , 2005; Lynch, 2004; Paez, 2004; Pao W. M., 2004; Shepard F. A., 2005; Shepard F. A., 2005). Unfortunately, these traits—alone or in combination--are not infallibly predictive of response to erlotinib and the absence of these characteristics is not a reliable indicator an individual will not respond to treatment (Balko, 2006; Nierendgarten, 2010; Perez-Soler, 2009); assuming either can lead to inappropriate over or under prescribing of erlotinib

If personal observations and clinical experience are not enough to accurately guide a physician's treatment decisions how can we improve the odds of selecting good candidates for erlotinib therapy (Printz, 2010)? As mentioned above, the presence of specific identifiable genetic mutations (changes) in the EGFR gene found in lung tumor tissue predict a patient's likelihood of benefitting from treatment with erlotinib (Eberhard, 2008; John, 2009; Levenson, 2008; Maemondo, 2010; Mok, 2009; Riely, 2006).

The EGFR gene signals cells to grow and divide; genetic abnormalities in the EGFR gene result in uncontrolled cell growth and proliferation leading to the formation of malignant tumors (Pennell, 2010). Erlotinib works by interfering with this processs (Bonomi, 2007; Johnston, 2006; Robinson, 2006; Shepard F. A., 2005).

Only 10 to 20% of patients in the U.S. with adenocarcinoma-type advanced or metastatic NSCLC tumors harbor genetic mutations in specific regions of the EGFR gene known to be associated with positive clinical response to erlotinib (Amler, 2005; Giaccone G. a., 2005; Keedy V. L., 2011; Lynch, 2004; Paez, 2004; Pao W. L., 2005; Tsao M. S.-R., 2005). However, not all patients with these mutations will benefit from the medication (Ciardiello, 2008; Giaccone G. a., 2005; Reck, 2010; Sequist L. V., 2008).

EGFR mutations can be detected using commercially available tests; the tests mitigate the need to rely solely on a physician's observations and clinical judgment based on phenotypic (observed) patient, tumor and demographic characteristics (Pennell, 2010). In this paper, the terms EGFR molecular testing, EGFR molecular mutation testing, EGFR mutation testing, EGFR testing, mutation testing, and biomarker testing are used interchangeably.

The FDA does not require physicians to perform an EGFR test before prescribing erlotinib (Genentech and (osi) oncology, 2011); physicians are free to prescribe it for any patient with lung cancer without restriction. But there are clear advantages to prospectively identifying patients who are more likely to respond to erlotinib, as well as those who lack the EGFR mutation and are unlikely to respond (Cataldo, 2011; Gazdar A. , 2010; Lennes, 2011; Maione, 2010; Printz, 2010; Shepard F. A., 2011; West J. H., 2010).

What are the implications of prescribing erlotinib for patients who are unlikely to respond to treatment? There are many, ranging from the costs associated with purchasing ineffective medication to unnecessary exposure to adverse drug effects to premature death. There are also significant risks associated with not treating patients who are likely to respond to erlotinib. People who benefit from erlotinib treatment often have a sustained period of progression free survival that is unlikely to be achieved with traditional chemotherapy. There is a "significant penalty in terms of overall survival" when patients with the EGFR mutation are treated with chemotherapy rather than erlotinib (West J. H., 2010). The opposite is true for people who do not have an EGFR mutation;

they have little chance of responding to erlotinib, which leaves chemotherapy as the only viable treatment option except for a very small number of patients who harbor other genetic mutations, which make them more likely to respond to other targeted therapies.

Although molecular tests that can identify specific mutations in the EGFR gene have been available since 2005, a recent study conducted by Julie Lynch, PhD, confirms EGFR mutation testing is vastly underused by oncologists practicing in the U.S. (Alt, 2011; Lynch J. A., 2013; Lynch J. A., 2013). A more recent publication suggests that EGFR testing rates may have improved slightly since the release of the Lynch study, but are far from optimal (Chustecka, 2013). Unfortunately, little is known about how oncologists decide what patients to test for EGFR mutations; experts have expressed opinions, but there are no published data available on the subject. The purpose of this dissertation is to begin identifying and understanding the factors influencing oncologists' decisions about using pretreatment EGFR tests. The results of the research outlined in chapter four along with the knowledge and insights gained during the literature review will be used to develop a plan for increasing pretreatment EGFR testing of patients with advanced or metastatic NSCLC.

CHAPTER 2 - LITERATURE REVIEW

The literature review conducted for this dissertation is very detailed and lengthy. Rather than including the complete literature review in this chapter of the manuscript, it has been moved to Appendix A to facilitate readability. Instead, this chapter contains a brief overview of the contents of Appendix A, which contains two parts and a summary. Part one has a detailed review of the epidemiology and etiology of lung cancer, as well as treatment options. It also contains a summary of the role tumor genetics play in treatment selection for patients with NSCLC, the availability of molecular tests that identify EGFR mutations that predict treatment response, and the low rate of use of EGFR tests by oncologists practicing in the U.S. Part two of chapter two includes a review of factors that influence and motivate physicians' behavior.

Part One: Understanding Non-Small Cell Lung Cancer and Treatments

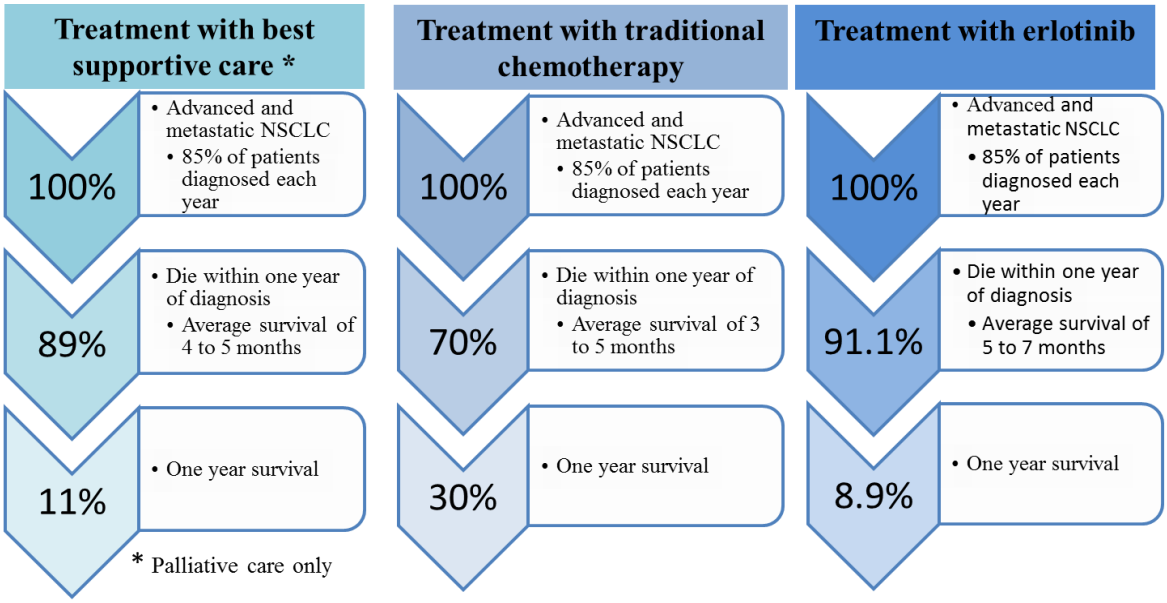
The effectiveness of traditional chemotherapy reached a plateau in the 1970s, leaving little hope for extended survival among those diagnosed with advanced or metastatic NSCLC (Breathnach, 2001; Maione, 2010). However, the tide began turning in the past decade with the launch of a small number of new oral targeted medications, including erlotinib, developed as a result of research into the genetic basis of lung cancer (Amler, 2005; John, 2009; Murdoch, 2008; Printz, 2010; Sequist L. V., 2008). The majority of patients who respond to erlotinib have a dramatic response resulting in remission that is sustained over a period of two to five years (Shepard F. A., 2005; Shepard F. A., 2005); unfortunately, the response rate in the general population of people treated for advanced or metastatic NSCLC is below 10%.

It is challenging for oncologists to correctly identify the individuals likely to respond to erlotinib. A number of early clinical studies involving the drug revealed patients with certain characteristics, including never smoking, female gender, Asian race, and tumors with adenocarcinoma

histology tended to have better response rates and treatment outcomes than individuals who lack these traits (Giaccone G. , 2005; Lynch, 2004; Paez, 2004; Pao W. M., 2004; Shepard F. A., 2005; Shepard F. A., 2005). As a result, these characteristics have become an informal guide for oncologists who are making treatment decisions for patients with NSCLC. While this approach is more accurate than relying on a physician's "gut feel", it often leads to inappropriate prescribing of erlotinib (Balko, 2006; Nierendgarten, 2010; Perez-Soler, 2009). Studies show less than one quarter of patients with advanced or metastatic NSCLC, including those with the characteristics listed above, have a mutation in the EGFR gene predictive of a positive response to erlotinib (Amler, 2005; Giaccone G. a., 2005; Keedy V. L., 2011; Lynch, 2004; Paez, 2004; Pao W. L., 2005; Tsao M. S.-R., 2005); of those, approximately half will respond to erlotinib (Printz, 2010).

Why is it important to select the right course of therapy initally when patients can be switched easily to another treatment regimen? Researchers predicted early on that response rates would be similar regardless of whether patients started on chemotherapy or erlotinib and then switched to the other when their cancer progressed (Brooks, 2012; Gandara, 2010; Gridelli C. B., 2008; West J. H., 2010; West J. H., 2010; West J. H., 2010). However, results of recent studies indicate the order of treatment—standard chemotherapy given first followed erlotinib or vice versa matters greatly with respect to treatment outcomes. People who have an EGFR gene mutation fare significantly better when treated with erlotinib first instead of chemotherapy; the opposite is true for people without a mutation. For example, patients without an EGFR mutation who received chemotherapy first had a 28% response rate vs. ten percent in those who received it second-line after failing to respond to erlotinib. More than half of patients started on erlotinib did not live long enough to be switched to chemotherapy.

Figure 1 - Survival Statistics for Advanced or Metastatic NSCLC



(Brooks, 2012; Gandara, 2010; Lennes, 2011)

Figure 2 - Treatment Paradigm for Patients with Advanced or Metastatic NSCLC

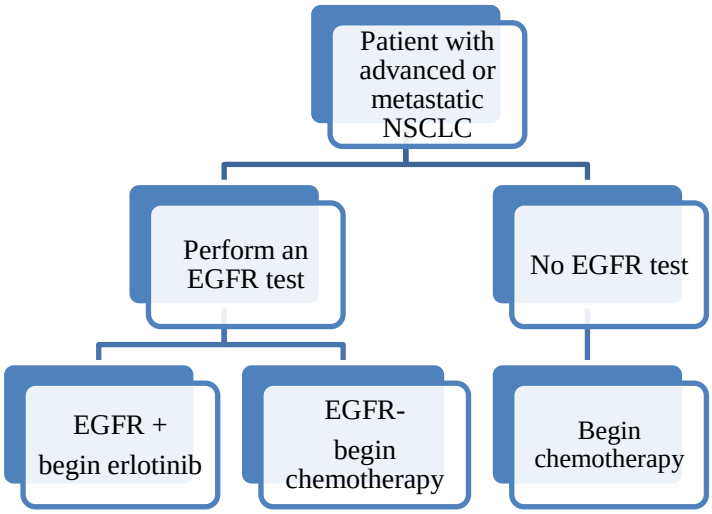
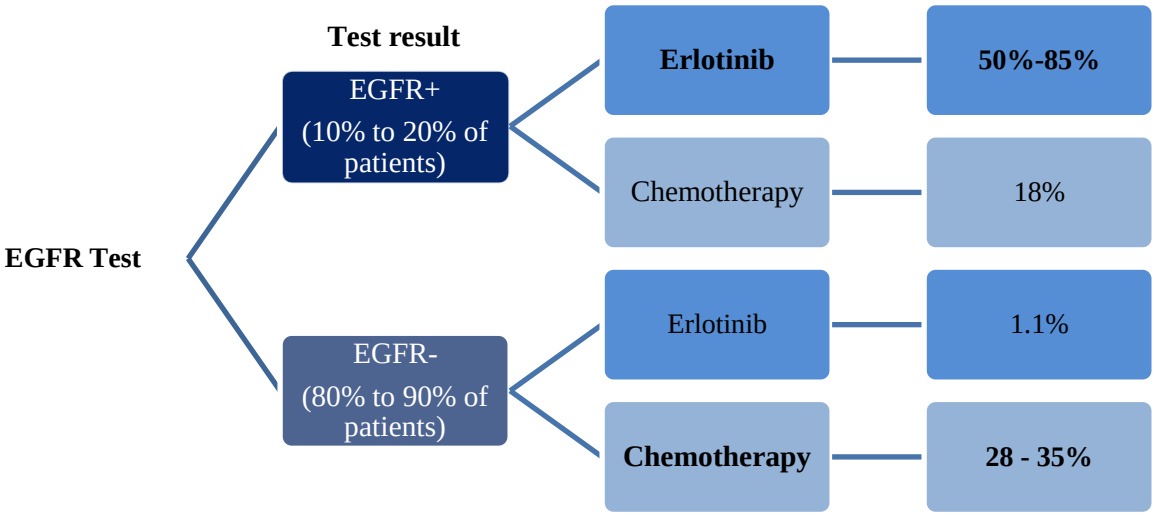


Figure 3 - Treatment Response Rates by EGFR Mutation Status



(Brooks, 2012; Gandara, 2010; Lennes, 2011; Mok, 2009; Rosell, 2012)

Although a growing body of published data confirms the benefits of prospective EGFR mutation testing of tumor tissue taken from patients with advanced or metastatic NSCLC, many oncologists continue treating every patient the same, as if NSCLC is a homogeneous disease (Gridelli C. B., 2008). Oncologists who understand individual patients may respond differently to erlotinib most often use the characteristics listed above to identify patients they think are more likely to respond instead of ordering EGFR tests to confirm their suspicions.

According to a study presented by Julie Lynch, PhD, at the 2011 American Association for Cancer Research (AARC) Cancer Disparities Conference, EGFR mutation testing is vastly underused by oncologists in the US even though it is a significantly more reliable predictor of treatment response than treatment decisions made on the basis of clinical judgment or observations alone (Alt, 2011; Lynch J. A., 2013; Shepard F. A., 2011). A recent article quoting Marc Ladanyi, MD, a lung cancer specialist practicing at Memorial Sloan Kettering Cancer Center, suggests testing rates may have improved somewhat in major cancer centers since the release of the Lynch data, but tests are still being significantly underutilized by oncologists practicing in community settings (Chustecka, 2013).

On paper, the choice seems clear, but obviously it is not or use of EGFR testing would be more widespread. There are obviously barriers to adoption of molecular testing, but there are no published data providing insights into the reasons why many oncologists choose not to order EGFR tests before prescribing treatment for their patients with NSCLC.

Part Two: Influencing Physicians' Clinical Behaviors and Decisions

Motivating physicians to change their clinical practice behaviors is no easy task (Grimshaw J. M., 2004; Lomas, 1989; Osarogiagbon, 2011; Roila, 2004; Satterlee, 2008; Wong R. K., 2012). There are a myriad of factors influencing change; some are positive and others are negative. Several factors were explored in part two of chapter two (see Appendix A); they are listed in the table below (Cochrane Effective Practice and Organisation of Care Group, 2012; Edwards, 2009; Flodgren G. E., 2011; Flodgren G. P., 2011; Freemantle, 1995; Giguère, 2012; Ivers, N., 2012; O'Brien, 2008; Pantoja, 2009; Satterlee, 2008).

Table 1 - Factors Influencing Physicians' Clinical Behavior

Facilitators of change	Barriers to change
✓ Federal legislation and regulations ✓ Institute of Medicine reports ✓ Lung Cancer Mutation Consortium and the Biomarkers Consortium ✓ Patient advocacy organizations ✓ Health care professional associations ✓ Payers/Managed care organizations (MCOs) ✓ Clinical practice guidelines	▪ Federal legislation and regulations ▪ Payers/MCOs ▪ Lack of motivation or time/clinical inertia ▪ Information and work overload ▪ Lack of knowledge or training in genetics ▪ Lack of buy-in for need to change ▪ Disagreement with proposed changes ▪ Perceived threat to personal autonomy ▪ Aversion to "cookbook" medicine ▪ Fear of genetic discrimination against patients by employers and insurers

There is no "magic bullet" for developing successful interventions aimed at motivating physicians to change their approach to diagnosing and treating specific diseases (Oxman, 1995). Developing formal clinical practice guidelines is an important first step in creating a path and rationale for change (Cabana

M. D., 1999; Wong R. K., 2012). However, motivating physicians to follow established guidelines remains a significant challenge (Aspinall, 2007; Freemantle, 1995; Fuchs, 2011; Green, 2007; Grimshaw J. M., 2012; Grimshaw J. M., 2004; Institute of Medicine, 2001; Oxman, 1995).

The Cochrane Collaboration has published a number of formal systematic reviews of published studies and literature reviews exploring the effectiveness of specific behavior-change interventions aimed at physicians (Cochrane Effective Practice and Organisation of Care Group, 2012; Edwards, 2009; Flodgren G. E., 2011; Flodgren G. P., 2011; Freemantle, 1995; Giguère, 2012; Ivers, 2012; O'Brien, 2008; Pantoja, 2009; Satterlee, 2008). The table below displays a summary of intervention types, along with their relative ability to motivate desired changes in physicians' behavior.

Table 2 - Interventions Aimed at Changing Physicians' Clinical Behavior

Intervention category	Magnitude of effect
Printed education materials (passive dissemination)	Small
Medical education meetings	
Didactic lectures	Small
Interactive sessions	Moderate
Didactic and interactive combined (no better than interactive alone)	Moderate
Educational outreach	Small to moderate
Opinion leaders	Large
Audit and feedback	Small to moderate
Reminders (paper and electronic)	Small to moderate
Financial incentives	
Limited duration contracts	No effect
Payment for each service, episode or visit	Small
Payment for providing care for a specific patient population	Small
Adhering to pre-specified treatment or quality targets	Small
Mixed systems	No effect

No single-pronged approach or combination of approaches works consistently and reliably to motivate changes in physician behavior. However, complex multi-faceted interventions combining several of the approaches listed above show promise.

The benefits of increasing use of EGFR testing are unmistakable and appear now to be irrefutable (Cataldo, 2011; Gazdar A. , 2010; Lennes, 2011; Maione, 2010; Printz, 2010; Shepard F. A., 2011; West J. H., 2010). Even so, adherence to clinical practice guidelines recommending routine use of EGFR testing remains much lower than might be expected after sustained efforts to motivate oncologists to adopt testing as standard practice when caring for patients with NSCLC (Alt, 2011; Chustecka, 2013; Lynch J. A., 2013).

There are a number of factors that can influence a physician's decision to use EGFR testing; however, little is known about how oncologists weigh various factors when making decisions. Chapter 3 describes the research methodology for beginning to identify the factors influencing oncologists' decisions about the use of EGFR tests when treating patients with advanced or metastatic NSCLC. The insights and understanding gained from this research and the literature review will help inform the plan for increasing the use of EGFR testing outlined in chapter five.

CHAPTER 3 - METHODS

Research Purpose

The goal of this research was to begin identifying factors oncologists consider when deciding whether to perform EGFR testing of lung tumor samples taken from patients with advanced or metastatic NSCLC. It was anticipated that some factors would be more important than others to individual physicians with some factors increasing the likelihood an oncologist will order an EGFR test for a specific patient and others weighing against testing.

Introduction

The Lynch data presented at the 2011 American Association for Cancer Research (AARC) Cancer Disparities Conference, and the subsequent publication of the research results in *Genetics in Medicine* in 2013, indicate EGFR mutation testing is vastly underused by oncologists treating patients with lung cancer in the U.S. (Alt, 2011; Lynch J. A., 2013). A pair of recent articles by Chustecka suggest testing rates may have improved in major cancer centers and academic medical centers since the Lynch data were published, but remain low in community oncology practice settings (Chustecka, 2013; Chustecka, 2013).

Although there is a significant body of evidence showing that using the molecular profile of a patient's lung cancer tumor is the most reliable method of selecting from among available treatment options, EGFR testing is seldom done in most geographic locations. Instead, treatment selection is usually based on clinical judgment or patient phenotypic (observed) characteristics, which are largely ineffective means of predicting a patient's likely response to erlotinib (Shepard F. A., 2011).

A thorough review of clinical and behavioral literature, medical media, and the Internet revealed no published data, qualitative or quantitative, identifying the reasons behind the variability in the use of EGFR testing by oncologists. Thought leaders in the lung cancer research and clinical practice communities--who treat a small percentage of cancer patients--have speculated about the reasons why other oncologists do not routinely use the widely available tests (Cataldo, 2011; Gandara, 2010; Hirsch, 2006; Lennes, 2011; Maemondo, 2010; Maione, 2010; Nierendgarten, 2010; Shepard F. A., 2011; West, 2010). However, experts were not the subject of interest in this research, nor do they appear to have any objective proof their opinions about the behavior and motivation of others reflect the actual beliefs and actions of their colleagues.

The research study was done to begin understanding why some community-based oncologists do not routinely perform EGFR tests; this step was necessary before a plan could be developed for motivating more routine use. Key informant interviews were used to gather data; the interviews provided an opportunity to hear directly from community oncologists who treat NSCLC about how they decide whether they're going to order EGFR tests for the patients they are treating. The interview format allowed the researcher to develop deeper insights and understanding than structured quantitative questionnaires or surveys. The interviews also facilitated deeper exploration into the thought processes, behaviors and perceptions of research subjects.

Ethics Approval

Ethics approval was obtained from the UNC Public Health-Nursing Institutional Review Board (study #13-2569, 7-26-2013), and verbal consent was obtained from each subject at the beginning of their interview.

Study Population

The research component of this disseration involved semi-structured telephone interviews with 18 to 20 practicing community oncologists. Because of the narrowness of the research topic, selective sampling was used to identify research subjects who have experience diagnosing and treating patients

with advanced and metastatic NSCLC. Because 85% of all individuals with NSCLC present with late stage disease, oncologists treating patients with lung cancer are higly likely to have extensive experience managing patients who are candidates for EGFR testing (American Cancer Society, 2013). Oncologists' experience treating this patient population was confirmed twice, once during the recruitment process and again at the beginning of the telephone interview.

A targeted strategy was used to identify research subjects. Oncologists were identified from the web sites of state oncology associations, community hospitals, oncology practices, and lung cancer advocacy groups; emphasis was placed on recruiting oncologists who treat patients with NSCLC in North Carolina and other southern states. Physician names were cross referenced to their medical practice web sites to identify prospectively—to the extent possible--oncologists who treat lung cancer and to confirm their contact information.

Jared Weiss, M.D., Assistant Professor, Thoracic, Head and Neck Cancer Programs, University of North Carolina Chapel Hill provided assistance and advice during the recruitment phase of the key informant interviews.

Study Recruitment

After a list of potential subjects was compiled, a personalized email (Appendix B) was sent inviting them to participate in the study. Oncologists who did not have published email addresses were recruited by telephone (Appendix C) instead of by email. The invitation had information about the purpose of the study, the type of information sought, details about the interview (e.g., length of time, recording), and communicated clearly that the research was being conducted independently without any external funding. The study was done in partnership with the Lung Cancer Initiative of North Carolina to increase the speed of recruitment. Oncologists usually have little free time for non-clinical activities; therefore, they were assured the interview would last no longer than 30 minutes.

Recipients were asked to respond by email or verbally indicating their willingness to participate in the interview and confirming they treat patients with advanced or metastatic NSCLC. Follow-up

telephone calls were made to anyone who did not respond to the initial invitation within a week. A second follow-up call was made three to five days later to anyone who still had not responded. A maximum of two follow-up telephone calls were made to oncologists who did not respond to the initial communication. Non-responders were considered non-contactable and were removed from the list of potential research participants.

Interview scheduling was done during the recruitment phone calls or in follow-up emails. An email confirmation was sent immediately to each participating oncologist with the date and time for the interview, along with the toll-free dial-in information and conference code. A final reminder email was sent to the oncologists 24 to 48 hours before the interview.

Interview Overview

After consent was obtained, the interviews began with a brief overview of the purpose of the study to help orient study participants to the task, along with the importance of their participation; they were reminded the interviews were being recorded so they could be transcribed verbatim for analysis purposes. Subjects were encouraged at the beginning and throughout the interview to elaborate when responding to questions. The interviews were semi-structured; the interview guide ensured the question wording and order were consistent across interviews.

A pseudonym was assigned to each participant and personally identifiable information was excluded from this manuscript to protect the confidentiality of study participants.

The interview guide had five sections, as shown below. The complete interview guide can be found in Appendix D.

Figure 4 - Interview Guide Overview
I. Introduction
II. Specialty and practice related questions
III. EGFR testing questions
IV. Closing
V. Thank you

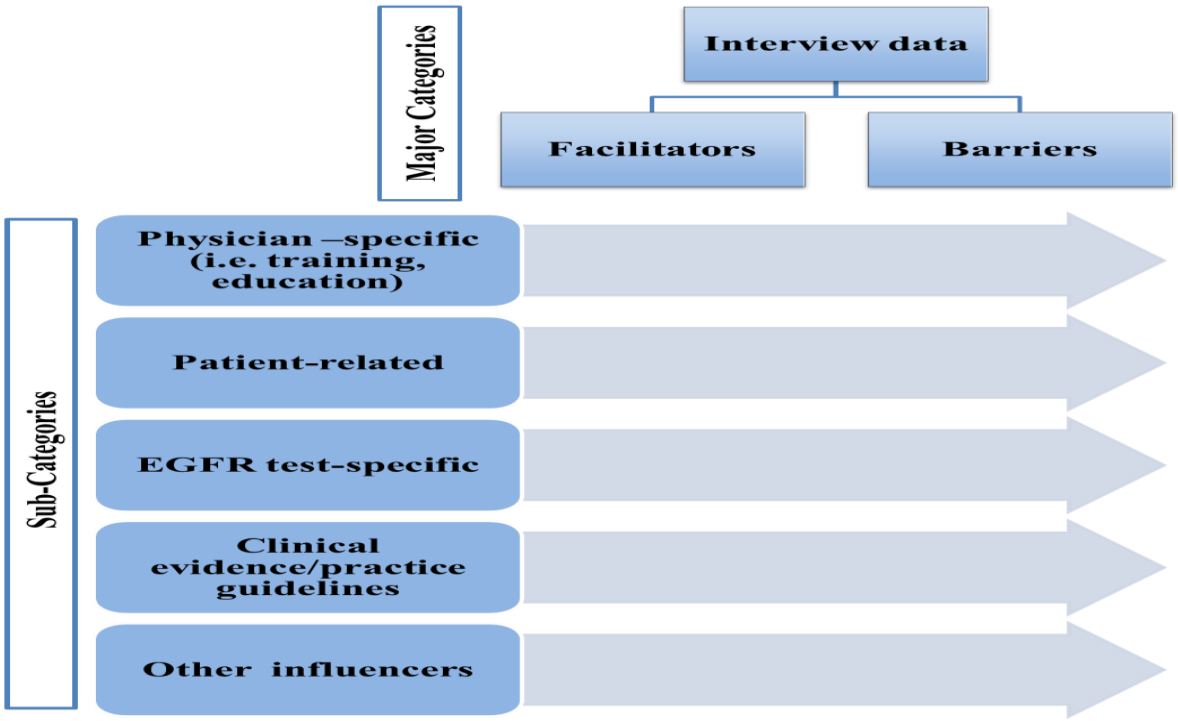
Telephone and Audio Recording Technology

The telephone calls were conducted using freeconferencecall.com, which provides free web-based conference call services and high quality audio recording capabilities eliminating the need for a separate recording device (Global Conference Partners). A small fee was paid to secure a toll-free dial-in number to eliminate any long distance fees for participants.

Analysis Plan

A deductive approach was used to identify a priori categories based on the research done during the literature review phase. Factors influencing a physician's decision to perform pre-treatment EGFR testing were separated into two broad categories and then further divided into sub-categories of factors an oncologist may weigh when making decisions about ordering EGFR tests for patients with advanced or metastatic NSCLC. The majority of the factors can influence a physician's decision to perform EGFR testing in either direction depending on the oncologist's perceptions, experiences, training, behaviors, and beliefs.

Figure 5 - Data Analysis Framework: A Priori Coding Categories



The audio recordings from the interviews were transcribed verbatim. The transcribed text was imported into MAXQDA 11, which is the qualitative data analysis software program that was used for coding the transcripts and content analysis (MAXQDA).

The researcher reviewed the transcribed interviews to confirm the presence of the two major categories and any factors that fit into the decision criteria/influencer categories displayed in the diagram above. No additional categories were identified during the coding and analysis processes; all factors mentioned by the key informants fit into the established data analysis framework.

A descriptive analysis of the research findings is presented in chapter four.

Study Limitations

A thorough literature search was conducted via the Internet using standard databases including PubMed Central, CINAHL, Cochrane Collaboration, ScienceDirect, Public Library of Science (PLoS), BioMed Central, Science.gov, FindArticles, and Medscape, along with the Google

Internet search engine. However, it is possible published or unpublished quantitative or qualitative research data or studies were missed during the investigation. In any event, the results of this research effort will add to any knowledge and data available on the subject.

The quality of the research in the reviewed literature about lung cancer and lung cancer treatments is very good; it provides relevant information supporting the need for and value of this research project. Information about factors influencing physicians' clinical behaviors and decisions discussed in part two of chapter two (Appendix A) is readily available. The number of studies evaluating specific interventions aimed at modifying the clinical behavior of oncologists is extremely limited; therefore, the literature review was broadened to include other medical specialists, including primary care physicians. It is possible research findings from studies done with physicians in other medical specialties are not generalizable to oncologists; there is no published research confirming or refuting the generalizability.

CHAPTER 4 - RESULTS

Subject recruitment was more successful than anticipated. Twenty-three (vs. 20 expected) community oncologists participated in the study. All interviews were conducted by telephone between August 19 and October 14, 2013, and were transcribed verbatim; the average length of the interviews was 19.5 minutes (range 11 to 26 min.). Data coding and analysis was performed using MAXQDA 11.

Key Informant Characteristics

All participants met the inclusion criteria. They all practice general oncology and currently treat patients with advanced or metastatic non-small cell lung cancer. All participants practice in the southern U.S. Over three-quarters (78%) are located in North Carolina; the remaining oncologists practice in Florida (1), Georgia (1), Louisiana (1), and Virginia (2).

Additional descriptive characteristics associated with the study cohort were captured during the interviews. All participants have completed their oncology training. The percentage breakdown by years in oncology practice is 39% (n=9) have been practicing ten years or less, 21.7% (n=5) between 11 and 20 years, 26% (n=6) between 21 and 30 years, and three have been in practice over 30 years. All of the oncologists practice in community settings; twenty are in private practice and three are employed by community-based non-profit hospitals. The average number of patients with advanced and metastatic NSCLC treated per month ranged from five to 50. Seventeen oncologists (74%) treat between five and 20 patients per month, three treat between 21 to 30 patients per month, two treat between 31 and 40 patients per month, and one treats an average of 50 patients per month.

Table 3 - Summary of Key Informant Characteristics

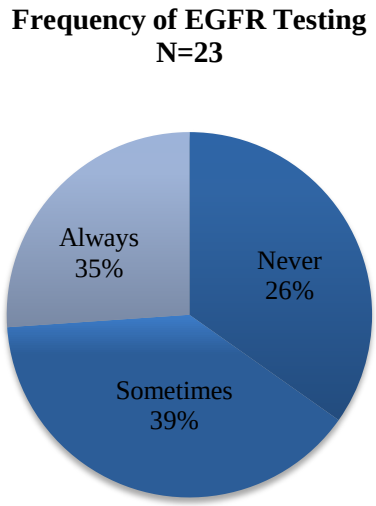
Characteristic	Frequency
Specialty - general oncology	23 (100%)
Practice location	
North Carolina	18 (78%)
Florida	1 (4.4%)
Georgia	1 (4.4%)
Louisiana	1 (4.4%)
Virginia	2 (8.8%)
Employment	
Private practice	20
Employed by a hospital	3
Length of time since completing oncology training	
0 to 10 years	9 (39%)
11 to 20 years	5 (21.7%)
21 to 30 years	6 (26.2%)
30+ years	3 (13.1%)
Average number of patients with advanced or metastatic NSCLC treated per month	
1-10 patients	8 (34.8%)
11 to 20 patients	9 (39.1%)
21 to 30 patients	3 (13%)
31 to 40 patients	2 (8.7%)
41 to 50 patients	1 (4.4%)
Percent of NSCLC patients with advanced or metastatic disease	
Up to 70%	6 (26.1%)
71 to 80%	8 (34.8%)
81 to 90%	7 (30.4%)
91 to 100%	2 (8.7%)

Frequency of EGFR Testing

The oncologists were asked about their frequency of use of EGFR testing (always, sometimes, never) when treating patients with advanced or metastatic NSCLC. Eight physicians

(34.8%) reported testing every patient; nine (39.1%) test some of their patients; and the remaining six (26.1%) never perform EGFR tests.

Figure 6 - Frequency of EGFR Testing



A Student's *t*-test (independent variables, one tailed, unequal variances (type 3)) was used to evaluate the characteristics and behavior-related information collected to determine which characteristics, if any, were significantly associated with oncologists who use EGFR mutation tests compared with those who do not. A p-value < .05 was considered statistically significant.

Having a higher percentage of patients with more severe NSCLC did not influence physicians' testing behaviors, nor did employment type (private practice vs. hospital, $p = .45$). However, oncologists treating a higher average number of patients with advanced or metastatic NSCLC per month were significantly more likely to test at least some of their patients ($p = .005$). Those who reported never using EGFR tests treat an average of 10 patients per month, those who sometimes order tests treat an average of 19 patients per month, and oncologists who always order tests treat an average of almost 22 patients per month. The difference in the average number of

patients treated per month between those who sometimes test compared with those who always test was not statistically significantly different (p = .309).

Time elapsed since completion of oncology training also had a significant impact on testing behavior. Of the nine oncologists who completed their specialty training within the past ten years, eight reported testing all of their patients and one tests some patients; this group was significantly more likely to perform EGFR tests than those who have been practicing oncology longer than ten years ($P < .05$). Five participants completed their training between 11 and 20 years ago; of those, three sometimes test patients and two never do. Five oncologists completed their training between 21 and 30 years ago; four of them test some patients and one does not. The three physicians who have been in practice over 30 years never order EGFR tests. All groups were significantly more likely to order an EGFR test than oncologists who completed their oncology training more than 30 years ago ($P < .05$).

Figure 7 - Testing Frequency by Years in Oncology Practice

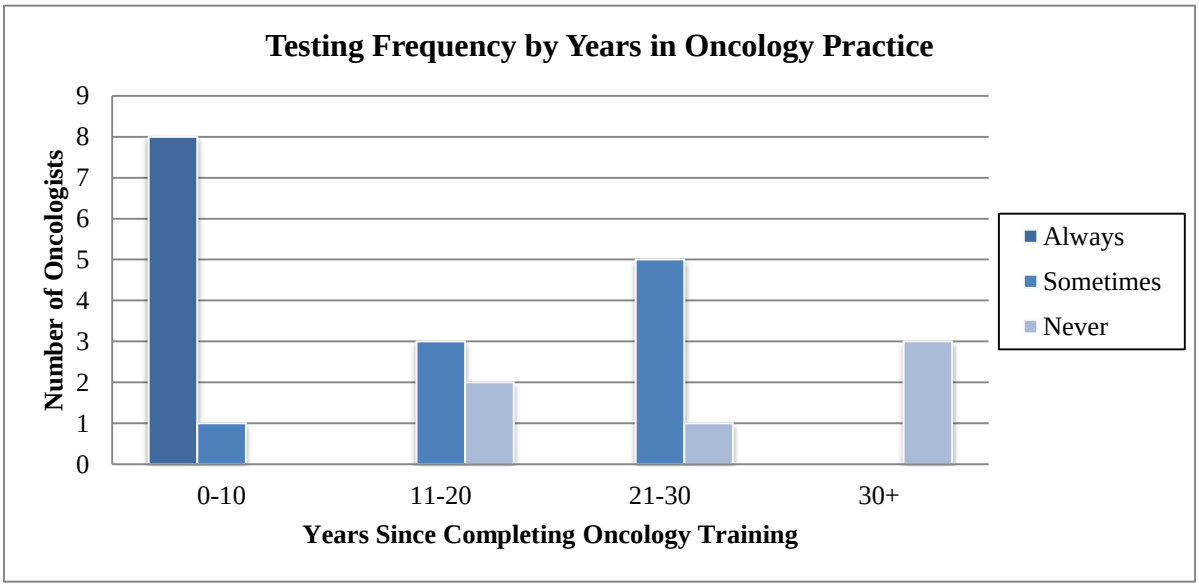


Table 4 - Characteristics and Their Impact on EGFR Testing Rates

Characteristic	Statistically significant difference in use of EGFR testing?	
	Yes	No
Percent of patients (higher vs. lower) with NSCLC with more severe disease		X
Employment type (private practice vs. hospital employee)		X
Average number of patients with advanced or metastatic NSCLC treated per month (higher vs. lower)	X	
Time elapsed since completion of oncology training (shorter vs. longer)	X	

Future Use of EGFR Testing

Physicians were asked, "Do you expect your future use of EGFR testing to increase, decrease, or stay the same?" No one was planning to decrease his or her use of EGFR testing in the future. Seventeen physicians expect their use to remain at the current level and six expect their use to increase or are unsure whether their use will increase or remain the same. The eight oncologists who routinely order EGFR tests for all of their patients expect to continue testing all of their patients. Of the nine physicians who test some patients, five expect their use will remain steady, two believe they will increase their use, and two are unsure. Four of the six (67%) physicians who report never using EGFR tests expect they will not begin testing patients; three of the four have been in practice 30 years or longer. The two remaining "never" respondents said they will begin testing in the future.

Facilitators and Barriers to Use of EGFR Testing

The primary goal of the key informant interviews was to learn directly from general oncologists the facilitators and barriers to their use of EGFR testing in the management of patients with advanced or metastatic NSCLC. Study participants were asked to identify the main reasons they do or do not order EGFR tests, as well as the most compelling drivers and barriers to testing. The influencers and barriers are discussed below and illustrated by quotes from study participants.

It was anticipated there would be sub-categories within the main categories of facilitators and barriers based on the literature review including physician-specific factors (e.g. training, experience); patient-related (e.g. health, willingness to be tested); EGFR test-specific (biopsy required, length of time to get results); clinical evidence and practice guidelines; and a general category for other influencers. These influencers can be classified as either facilitators or barriers depending on the responses provided by individual physicians. While influencers falling into all of categories were mentioned during the interviews, some were mentioned much more frequently than others were. The clinical literature and practice guidelines category dominated the facilitators named by oncologists who perform EGFR tests and two different categories--patient-related and physician-specific factors--dominated the barriers cited by those who sometimes or never perform EGFR tests.

Facilitators of EGFR testing. Oncologists who reported testing some or all of their patients were asked, "What are your main reasons for ordering EGFR mutation tests for your patients?" and "Is there any one thing that stands out in your mind as a particularly compelling reason to test your patients?". The six oncologists who never test patients were not asked these questions; however, one of them mentioned during the interview they would consider testing at least some patients if a trusted colleague recommends it.

Clinical literature and practice guidelines. This was the most frequently mentioned factor influencing the decision to use EGFR testing. The eight oncologists who always test and seven of the nine who test some patients mentioned clinical literature and practice guidelines as the most compelling reason to perform pretreatment EGFR testing because it has been shown definitively that testing results in better treatment outcomes; it also provides a degree of confidence when making treatment decisions. The following quotation is representative of the responses gathered from these 15 physicians, "The clinical literature is clear that choosing treatment based on the EGFR status of patients with advanced non-small cell lung cancer produces the best outcomes. Patients with EGFR mutations can have a dramatic response to erlotinib but those without a mutation get better results

with chemotherapy. Not only do EGFR test results guide my first treatment decision, they provide guidance for follow-on treatment."

Two participants mentioned following the National Comprehensive Cancer Network (NCCN) treatment guidelines for non-small cell lung cancer.

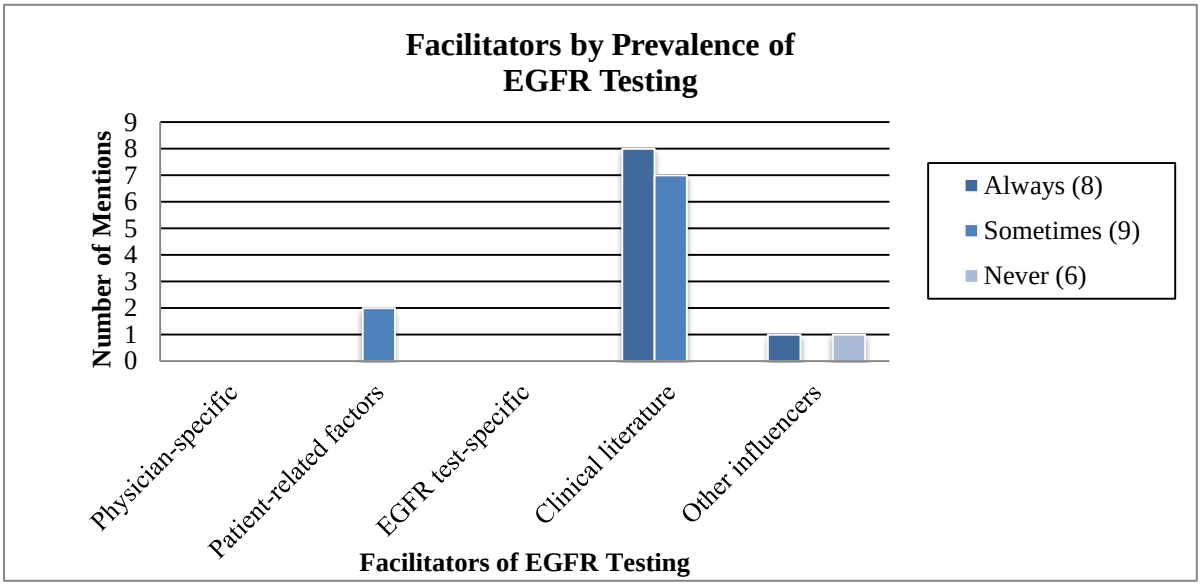
Even when probed for additional reasons for ordering EGFR tests, none of the participants mentioned any other factors that influence their decisions.

Patient-related factors. Of the two remaining oncologists who test at least some patients, one tests only those patients who ask to be tested and the other tests only those patients who prefer to use oral therapy over chemotherapy to determine prospectively whether the patient has an EGFR mutation that would make them more likely to respond to treatment.

Other influencers. One of the eight oncologists who test all of their patients mentioned that testing is done reflexively (automatically) by the pathology department on all NSCLC tissue biopsies performed at their local hospital. "I don't even have to think about it. It was not always this way. My partners and I worked with the hospital pathologist to get it done automatically. It's the right thing to do based on the clinical literature." One oncologist who tests some patients was motivated to start ordering EGFR tests after it was recommended by a respected colleague.

Physician-specific and EGFR test-specific. None of the responses fell into either of these two sub-categories.

Figure 8 - Facilitators by Prevalence of EGFR Testing



Barriers to EGFR testing. All study participants--including those who reported always ordering EGFR tests--were asked the following two questions, "What is the main reason or reasons you decide not to order an EGFR mutation test for a patient?" and "Is there any one thing that is the most compelling reason for not testing your patients?". The eight oncologists who test all of their patients were also asked the questions to determine if there is any situation that causes them to avoid testing a patient. All responses were grouped into the five sub-categories mentioned above.

Patient-related factors. The health of a patient plays a significant role in the decision not to perform EGFR tests for many physicians; it was the most frequently mentioned barrier to testing. Of the eight who reported testing all of their patients, all but one reported there are patient-specific circumstances that preclude testing, including patients who are too sick to undergo a biopsy; those who are in hospice care or actively dying; and those who refuse to be treated. One physician tests every patient—including those in hospice—because individuals with an EGFR mutation are highly likely to respond to targeted treatment regardless of their health status. If a patient tests positive for an EGFR mutation, they are withdrawn from hospice and started on erlotinib. Patients who do not harbor an EGFR mutation remain in hospice. All of the nine doctors who test at least some of their

patients cited similar situations where they avoid testing; in addition, this group also mentioned other factors, including: the physical condition of the patient (frailty); patient refusal to be tested; lack of (patient) understanding of the importance of EGFR testing; and pressure from the patient and patient's family to begin treatment immediately.

Physician-specific factors. Of the oncologists who sometimes or never use EGFR testing, the nine who sometimes test (100%) and four who never test (67%) used a variety of words and phrases that suggest they are confident in their ability to select the best treatment for a patient based on their clinical judgment and experience; this was the second most frequently cited barrier to EGFR testing. The following three quotes are illustrative of the self-confidence theme. "I really don't need to test most of my patients because I rely on previous experience to select the best treatment for a given patient." "I don't believe it is necessary. There is data showing testing is a nice to do but not necessary." "I'm not convinced testing a patient is any better than using my clinical judgment. I've been doing this a long time. I believe I know what is best for the patient, so there is no reason to test them."

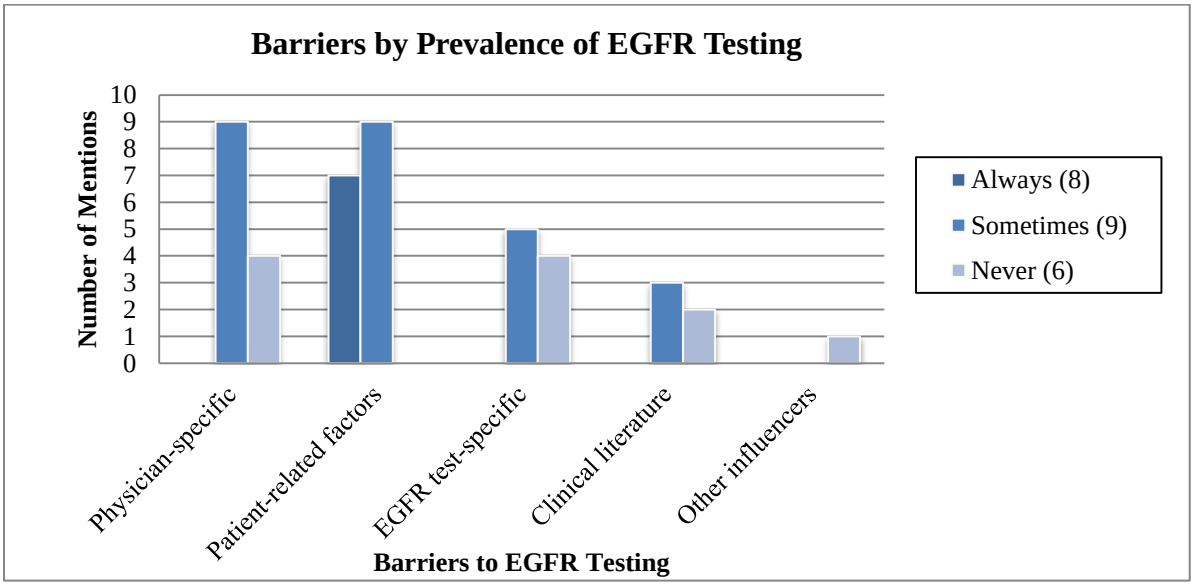
The two other physicians who never test patients said they do not know enough about EGFR testing to make a well-informed decision about using it. None of the oncologists who test all of their patients mentioned any physician-specific factors.

EGFR test-specific factors. Test-related factors were mentioned by 9 physicians (5 sometimes and 4 never testers); they included cost, length of time it takes to get results, the need for a biopsy, and insufficient tissue available to perform the test. The following quote is from an oncologist who decided to give testing a try and subsequently decided the downsides of testing outweigh the benefits, "I did it a couple times but found it to be a big hassle. It requires a good biopsy and we have to send the sample out to be tested by a lab. It takes time to get results and in the meantime, people are not being treated. I don't think that's a good way to practice medicine."

Clinical evidence and practice guidelines. Five oncologists—including three who test some patients and two who never test—indicated a need for additional proof that EGFR testing leads to better treatment outcomes. One doctor who tests some patients said, "I would say that it's too soon to tell if using EGFR testing is going to help my patients so I'm not ready to test everyone. If I'm going to start someone on chemotherapy there's no reason to test." Another mentioned, "Guidelines are just that, guidance and are not required." A third oncologist who never uses EGFR testing said, "I need more proof that testing is worth the effort."

Other influencers. One oncologist who does not use EGFR testing mentioned that no colleagues do it either.

Figure 9 - Barriers by Prevalence of EGFR Testing



Discussion

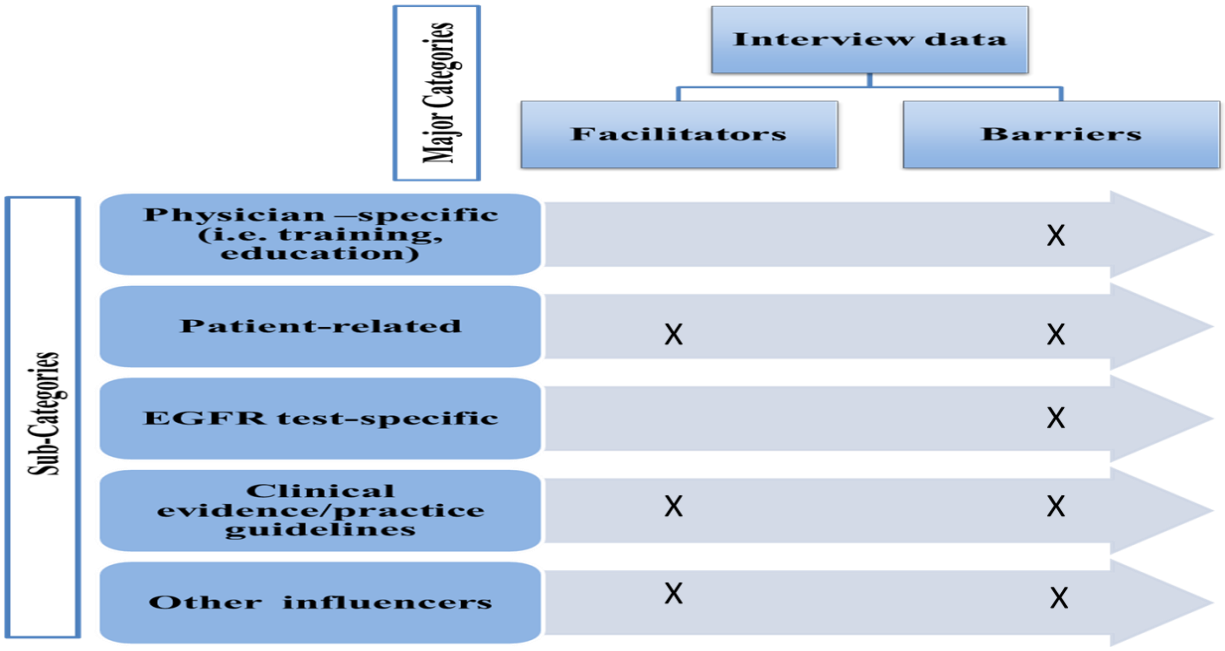
Twenty-three general oncologists who practice in community settings participated in the key informant interviews. They all practice in the southeastern US and completed their oncology training prior to being interviewed. Participants were asked whether they always, sometimes or never perform

EGFR tests on patients with advanced or metastatic NSCLC. Eight of the twenty-three reported testing all of their patients, nine test some patients, and six never use the test.

Having a higher percentage of patients with NSCLC who have advanced or metastatic disease and employment situation—private practice vs. being employed by a hospital—did not influence the likelihood of performing EGFR tests. However, two characteristics were associated with an increased likelihood of performing EGFR testing on at least some patients; these included treating an average of more than ten patients with advanced or metastatic NSCLC a month, and length of time since completion of oncology training. Oncologists who have been in practice ten years or less were significantly more likely to test at least some patients than physician who have been in practice longer; those who have been in practice over 30 years were the least likely to use EGFR testing.

The factors influencing a physician's decision to perform EGFR testing were categorized as facilitators or barriers. In addition to these two main categories, five sub-categories were identified a priori, including: physician-specific factors (e.g. training, experience); patient-related (e.g. health, willingness to be tested); EGFR test-specific (biopsy required, length of time to get results); clinical evidence and practice guidelines; and a general category for other influencers. Participants mentioned three categories of facilitators (patient-related, clinical evidence and practice guidelines, and other influencers) and all five were cited as barriers.

Figure 10 - Summary of Category Mentions by Key Informants



The most commonly mentioned facilitator was clinical literature and practice guidelines, and the second most common was patient-related factors, followed by other influencers. The most commonly mentioned barrier was patient-related factors, followed by physician-specific, test-specific, clinical literature and guidelines, and other influencers. A consistent theme emerged during the discussion of barriers to testing. Thirteen physicians, including all nine "sometimes" testers and four "never" testers used words and phrases suggesting they are confident in their ability to make the best treatment decisions for their patients based on their clinical judgment and experience, which obviates the need for EGFR testing.

Study Limitations

A thorough search of the Internet suggests this may be the first study done with the intention of understanding the factors that influence a community oncologist's decision about performing EGFR mutation tests on patients with advanced or metastatic NSCLC. The key informant interviews provided the opportunity for oncologists to share their personal experiences, beliefs, and behaviors in

their own words in a confidential setting. However, time and resource constraints limited the number of interviews that were conducted.

Twenty-three community-based oncologists participated in the study. The study participants were purposely selected for their knowledge and experience treating lung cancer patients; they all practice oncology in the southern U.S. Therefore, the cohort may not be representative of community oncologists practicing throughout the U.S. Based on time and resource constraints, the number of key informant interviews was limited. It is possible there are additional factors influencing oncologists' decisions about EGFR tests that were not identified during the interview process. In order to increase the reliability and generalizability of the data, it is important that a larger study involving more oncologists across a wider geographic area and with a greater variety of practice types be conducted in the future.

Despite the limitations outlined above, the data collected combined with information uncovered during the process of researching and writing the literature review (Appendix A) provided sufficient guidance for creating the plan for increasing the pretreatment use of EGFR testing that is presented in chapter five. Kotter's eight-step process for change was used as the framework for developing the implementation plan.

CHAPTER 5 – THE IMPLEMENTATION PLAN

The findings of this study, although not generalizable, provide valuable insight into the thought processes of community oncologists treating patients with late stage NSCLC. These data, along with information gathered during the literature review, provide a foundation for formulating an approach for increasing the use of EGFR testing based on John Kotter's eight-step process for change, which was originally described in his book, *Leading Change* (Kotter, 1996). Each of Kotter's eight steps, including creating a sense of urgency, forming a powerful coalition, creating a vision for change, communicating the vision, overcoming obstacles, creating short-term wins, building on the change, and anchoring change in the culture are discussed in detail below.

Interventions will be aimed at three target audiences, including community oncologists; other healthcare professionals; and lung cancer patients, their families, caregivers, and advocates. Not all of Kotter's steps apply to the all three constituencies.

Implementation Plan

This implementation plan focuses on increasing the use of EGFR testing in the state of North Carolina. The majority of community oncologists interviewed for this research practice in North Carolina; they provide a window into the perspectives and behaviors of others who practice here. Why am I starting on a small scale, given the magnitude of the problem? The literature review covers a wide range of interventions used commonly to motivate physicians to change their clinical practices and habits (Table 2, p. 13); very few are consistently successful and most have limited impact. Because literature on clinical practice behaviors of oncologists was scarce, the information regarding the impact of various tactics included in this dissertation came primarily from studies conducted with physicians in other specialties. Initial efforts within North Carolina will provide data specific to the

impact of interventions on EGFR testing rates, albeit on a small scale. Each tactic implemented in the NC pilot will be evaluated after completion to identify interventions that work best to motivate an increase in EGFR testing by community oncologists before rolling them out to a broader audience. Nationwide outreach and education efforts are extremely expensive and it is highly unlikely sufficient funding will be available without proof that tactics used produce meaningful results. Using a pilot approach provides an opportunity to evaluate tactics and collect the data necessary for fundraising to support a national campaign. It also conserves resources by avoiding ongoing use of tactics that do not produce meaningful results.

Creating a Sense of Urgency

Creating a sense of urgency is the crucial first step for initiating change. There are compelling reasons for increasing the rate of EGFR testing. The first step in creating a sense of urgency is making professional and patient groups aware that there is a variance in testing rates and sharing the facilitators and barriers to testing uncovered during this research. Eight of the oncologists interviewed reported testing all of their patients; they were uniformly shocked to learn that many of their colleagues do not. These oncologists consider testing to be the standard of care and assume all of their colleagues concur. Responses from these eight oncologists suggest that oncologists who are in the position to help reverse the trend might not even be aware of the existing disparities; making them aware of the published data and these research results is a critical step in beginning the process of change.

Background information about the variation in testing rates and the study results will be shared with the North Carolina Oncology Society (NCOS), the statewide professional organization for oncologists. This information will allow them to participate in developing training and educational programs aimed at breaking down barriers to testing. I will enlist the help of Dr. Weiss who provided assistance and advice during the recruitment phase of the key informant interviews, and Dr. Jennifer Garst, M.D., a lung cancer specialist practicing at the Duke Raleigh Cancer Center, Raleigh, NC, who is a member of the Board of Directors of the Lung Cancer Initiative of North

Carolina. They are members of NCOS and are in a position to provide advice on the best way of capturing the attention of the appropriate individuals in NCOS to help speed access and sharing of information.

The Lung Cancer Initiative of North Carolina (LCI), an advocacy organization, was a partner in this research. They have seen the results and already have a sense of urgency about this issue because they understand testing impacts the quality of care received by lung cancer patients in North Carolina. I presented the study results to LCI members including patients, advocates, and health care professionals at their annual meeting and volunteer recognition dinner held on February 9, 2014, in Durham, North Carolina. I am working with LCI to explore ways of breaking down barriers to testing from both the physician and patient perspectives.

Genentech, the pharmaceutical company marketing erlotinib has asked me to share the study results with them. They understand the importance of tying the prescribing of erlotinib to EGFR testing results so that patients get the best possible treatment even if it results in the prescribing of other medications (Genentech, 2014). Genentech will be part of the planning process and will help implement the integrated plan for increasing EGFR testing rates. Pfizer, another pharmaceutical manufacturer has also expressed interest in learning more about this study and participating in efforts to increase molecular testing rates. Admittedly, pharmaceutical companies are interested in this research because it will help them increase sales, but their participation and support also serves the greater good of increasing testing rates.

Forming a Powerful Coalition

A well-established patient advocacy group (LCI) and a professional organization (NCOS) already exist in North Carolina. They collaborate and cooperate on efforts to decrease death from lung cancer and improving quality of care and life for people with lung cancer through research, awareness, education and access programs. The NCOS has an ongoing advocacy program supporting

state funded cancer initiatives (North Carolina Oncology Society). The LCI is the only established advocacy organization focused specifically on the care of lung cancer patients in North Carolina.

Pharmaceutical manufacturers provide significant financial, educational, and logistical support to these two organizations. For years, drug companies were opposed to testing, which they saw as limiting the use and revenue for targeted therapies. However, they are now supporting efforts to increase molecular testing for EGFR and other mutations that predict response to specific treatments. Together, the LCI and NCOS, with support from pharmaceutical manufacturers, and individual and corporate donors have the combined resources and contacts to reach a large number of community oncologists and lung cancer patients in North Carolina. The first step, however, is for them to commit to working together to create complementary initiatives for influencing physicians and patients to establish a dialogue about EGFR testing, regardless of who initiates the conversation.

Drs. Garst and Weiss are active members of both North Carolina-based organizations and are in the best position to bring them together to tackle this problem. I will ask them to facilitate a meeting between the two organizations and personnel from pharmaceutical companies to establish an EGFR testing task force to begin working on a vision and plan for increasing the use of EGFR testing in North Carolina. I will be a founding member of the task force.

Creating a Vision for Change

This research provides extra impetus for change because, for the first time, specific facilitators and barriers to testing were uncovered and can be addressed. The LCI and NCOS already support and communicate the importance of pretreatment EGFR testing to their members. However, working together on the EGFR testing task force, and with other partners, they can make a bigger impact than working alone. In addition to having people representing different perspectives and constituencies, task force members must have a variety of complementary skills, including strategy, marketing, and implementation in order for the group to be successful.

The first responsibility of the task force will be developing a vision statement to guide the work of the group. A vision statement is the formal statement of an organization's purpose in the context of its values; it helps ensure all members are working toward the same end, which facilitates cooperation and achievement of the vision. Creating a vision statement without expert guidance is more difficult than it seems, and often results in a confusing combination of vision, mission, and values statements. I will ask Leslie Burnside, MHA, who is an expert in visioning, to work with the task force to develop a powerful vision. She will also help develop a mission statement defining the purpose of the group.

Having a vision and mission is not enough—the task force must also establish overarching objectives supporting achievement of the group's vision and mission. The objectives will be specific, measureable, attainable, reasonable, and time bound. Without shared objectives, task force members could go off on their own, undermining the value of forming a guiding coalition to tackle this issue.

Communicating the Vision

The task force will develop a comprehensive communications plan supporting the achievement of the overarching objectives; the various tactics in the plan will be integrated so they build on each other to maximize impact and motivate desired behavior. Every tactic in the plan will have measureable objectives ensuring tactics contribute to achieving the group's overarching objectives. In addition to other measures, the task force will ask manufacturers of EGFR tests to provide monthly counts of tests performed in North Carolina, which will be monitored for changes over time. The tactics achieving their objectives will be implemented on a national level as soon as possible without waiting for completion of other tactics in the communications plan; this approach facilitates a faster ramp-up on a broader scale. Tactics not producing the desired results will be discontinued to minimize wasteful expenditure of human and financial resources.

One of the strategies in the communications plan is for task force members to communicate results of the study, along with the vision, mission, and objectives of the task force to the leaders and

members of their respective organizations, as well as to the broader lung cancer community. A press release explaining the work of the task force, summarizing study results, and providing directions about how and where to obtain an EGFR mutation test will kick off implementation of the plan. The release will be sent to the news and health editors at all media outlets (print, broadcast, and digital) in the state of North Carolina. Follow-up phone calls will be made to news organizations pitching the story and making task force members and others available for interviews. All spokespersons will be media trained to ensure they can communicate the key talking points effectively.

Overcoming Obstacles

As noted in chapter 4, there were a number of barriers mentioned during the key informant interviews. The task force will take a strategic multi-pronged approach to overcoming the barriers by targeting communications to a number of audiences, including community oncologists, other healthcare professionals, and patients and their families, caregivers, and advocates.

Community Oncologists. Oncologists who test some patients are likely to be easier to motivate than those who never test. They may simply be unaware EGFR testing improves outcomes for all patients, not just those with a mutation. On the other hand, 87% of oncologists interviewed who test some or none of their patients expressed confidence in their ability to make the best treatment decisions for their patients based on their clinical experience and judgment alone. Clinical literature indicates their confidence is misplaced. Unfortunately, a majority of never and sometimes testers interviewed reported having no intention of adopting or expanding their use of EGFR testing, suggesting that it will take a significant amount of effort to motivate them to change their behavior**.**

There are two main approaches for increasing the use of testing; one is using direct influence on community oncologists and the other is using indirect methods of influence. The task force has more control over the medium and message when communicating directly with this target audience

than when using third parties—including pathologists, hospital laboratory managers, oncology nurses, and patients—to influence community oncologists.

Some physicians interviewed want more proof EGFR testing produces better outcomes and others admitted to being ill informed about testing. It is clear from the responses education is an essential strategy for increasing the rate of testing. Oncologists must have knowledge and understanding of the critical role testing plays in delivery of high quality care before they can be motivated to use it. What tactics should be used for educating oncologists? As noted in the literature review, there is substantial variability in the impact of change efforts, which indicates a need to offer a range of educational experiences in a variety of settings and formats. When creating the communications plan, the task force will focus on interventions known to have a higher likelihood of successfully motivating behavior change in physicians.

Peer influence is arguably the most reliable method of influencing physician behavior. Identifying and including local and regional thought leaders in the planning stage will help ensure their alignment with the vision and mission of the task force. Task force members have relationships with oncologists who practice in North Carolina; they will use their networks to identify and engage oncologists respected by their peers. Members of the task force will decide who among them is best suited to recruit individual thought leaders to participate in the outreach efforts. The thought leaders recruited will be asked to take advantage of any opportunity—casual or formal--they have to talk to peers about the importance of molecular testing.

Thought leaders will be invited to collaborate with the task force on development of develop two turnkey communication kits—one for professional audiences and one for consumers. The kits will include customizable templates for event invitations and awareness posters; a customizable program announcement for distribution to local media outlets; slides; draft agendas; talking points; handouts; and a list of speakers. Kit components will be able to be used in any combination depending on circumstances and specific audience needs. The kits will facilitate delivery of

consistent, concise and compelling communications regardless of the sophistication of the audience. Studies show interactive educational methods are more effective at motivating behavior change than passive methods or a combination of the two; therefore, the kits will include interactive exercises for use in engaging audience members during presentations.

One issue that has not yet emerged in the literature or during my research, but that would add weight to the argument in favor of testing, is the threat of medical malpractice lawsuits based on the failure to perform and base treatment on results of molecular testing. I will ask Dean Harris, a member of the faculty of the Gillings School of Global Public Health, to recommend individuals who are knowledgeable about medical malpractice law and may be willing to research whether any such lawsuits exist. If there has been successful litigation, the issue of legal liability will be woven into the messaging for targeted healthcare professional audiences because anyone participating in the direct care of patients with NSCLC is vulnerable to legal action.

In addition to peer influence, other means of communicating directly with community oncologists will be used. Pharmaceutical companies participating in the task force have sales representatives that meet regularly with community oncologists with a goal of influencing physicians' clinical behavior (primarily prescribing). These companies also deploy non-sales field-based medical science liaisons (MSLs) that have responsibility for establishing relationships with influential physicians and researchers, and sharing science-based information with them (Cutting Edge Information, 2012). MSLs can more effectively educate and motivate change because they are healthcare professionals with expert knowledge in specific therapeutic areas, which increases their credibility. Physicians expect the sales representatives and MSLs calling on them to share new and interesting information, which provides the perfect opportunity for sharing clinical data about the importance of EGFR testing. Information contained in the professional kit can be repurposed for use in sales materials and tablet-based education.

The task force will also work with the North Carolina Health Education Centers (AHEC) to fund and develop an accredited live continuing education program for doctors and nurses practicing in NC (NC AHEC, 2014). AHEC is one of the leading providers of continuing education programs for health care professionals working in NC; their mission includes enhancing the quality of care and health outcomes for residents of North Carolina. The program office, which is responsible for developing educational programming, is located on the campus of the University of North Carolina Chapel Hill. AHEC has 10 regional centers across the state allowing them to increase access and ease of participating in educational programs and conferences. The task force will supplement AHEC's publicity efforts to increase awareness of the continuing education programs and boost attendance.

Many oncologists interviewed avoid testing patients in hospice care because, by definition, patients in hospice receive palliative care instead of potentially curative treatment. However, one oncologist interviewed tests patients in hospice that have not yet been tested because individuals with one or more specific EGFR mutations often have an almost immediate, profound, and sustained response to erlotinib treatment. Testing patients in hospice gives them a chance at living significantly longer with good quality of life. Sharing this oncologist's approach will likely resonate most with oncologists who already test some or all of their patients. After presenting results of my research at the LCI meeting on February 9, two oncologists in attendance mentioned that testing patients in hospice had never occurred to them, but they are planning to start doing so immediately, which is exactly the response I am hoping to get when we begin actively educating community oncologists. Information about testing patients in hospice will be included in both kits. Patients, families and caregivers are important audiences for this information because it will help them have the confidence to ask their oncologist to be tested. The community oncologist who tests his patients in hospice care has volunteered to participate in our education efforts.

Other Healthcare Professionals. There are healthcare professionals that can influence community oncologists in a variety of ways to increase their use of EGFR testing.

Pathologists. Pathologists analyze and perform tests on tissue extracted during biopsy procedures. Pathologists can increase the use of EGFR testing in two ways. First, they can use their personal and professional relationships, and position in the hospital to motivate community oncologists to create standing orders for EGFR testing of tumors confirmed to be NSCLC. The second way is by instituting reflexive testing, which is automatic ordering of laboratory tests based on a specific diagnosis or results of an initial test (Eastep, 2011). Reflexive testing does not require any action by oncologists; it is an institutional protocol triggered by the presence of certain tumor characteristics.

In June 2013, the College of American Pathologists published an evidence-based guideline recommending using EGFR testing to inform prescribing of targeted therapies for the treatment of NSCLC (College of American Pathologists, 2013). Pathologists can use this guideline as proof of the value of EGFR testing, along with results of published studies. Task force members will work with the North Carolina Society of Pathologists (NCSP) to leverage professional kit contents for use by the Society and pharmaceutical sales representatives to educate pathologists practicing in community hospitals about the importance of routinely performing EGFR mutation tests. The materials will urge pathologists to proactively engage community oncologists in conversations about the role and importance of EGFR testing, and consider instituting reflexive EGFR testing in their hospitals. The NCSP members will be made aware of AHEC continuing education programs so they can publicize the events to their medical colleagues.

Directors and Managers of Hospital Laboratories. Managers of hospital laboratories play a critical role in deciding what laboratory tests will be available for their inpatients and outpatients. The Clinical Laboratory Management Association (CLMA) has a chapter in North Carolina (Clinical Laboratory Management Association, 2014). The task force will reach out to the Carolina chapter to

get their input on the best way of encouraging members to be proactive about educating community oncologists about EGFR mutation testing and instituting reflexive molecular testing for appropriate lung cancer patients. They will be encouraged to work with their hospital's pathologist to combine resources to increase the effectiveness of their efforts.

Oncology Nurses. Oncology nursing is a recognized nursing specialty. Oncology nurses play a pivotal role in the direct delivery of cancer care to patients. They often develop very close relationships with their patients, patients' families and caregivers and, in general, spend more time with patients than do oncologists. Because of the trust established through repeated patient contact, oncology nurses have the credibility to talk to patients about the importance of molecular tumor testing and motivate patients to ask for testing if it has not already been done. The interview responses suggest patients may be able to motivate their oncologist to do an EGFR test simply by asking for it.

In addition to nursing education offered by the regional AHEC chapters, the Oncology Nursing Society (ONS) is an important educational resource for oncology nurses (Oncology Nursing Society, 2014); there are six chapters in North Carolina. The vision and mission of the ONS are consistent with the task force's initiative. The task force will work with the North Carolina chapters of the ONS to use kit contents and components to develop educational materials and programs about molecular testing for their members; they will also help AHEC publicize their continuing education programs through the ONS chapters.

Patients and Their Families, Caregivers, and Advocates. Seven of the eight oncologists who test all of their patients and all nine of the oncologists who test some of their patients mentioned patient-related issues during the barriers section of the interview. None of the oncologists who never perform EGFR testing mentioned any barriers falling into this category. Some barriers are insurmountable and some are potentially modifiable. Some patients are too frail or sick to undergo the biopsy procedure needed to obtain a tumor sample for testing, and others are actively dying. Some patients refuse testing or more treatment. Some refuse testing because they want to start

treatment immediately and do not want to wait to get test results to begin. Study participants said this is the primary reason families often push to move forward with treatment without testing.

The goal of the consumer kit is increasing awareness of EGFR testing, motivating patients to be tested, and facilitating patient and provider discussions about testing. The kit contents will communicate information in easy to understand language and graphics. The task force will develop multi-language print materials (e.g. brochures, posters) and educational video content for use in oncologists' offices and oncology clinics, patient and community education programs, and health fairs. Pharmaceutical sales representatives and MSLs will assist by distributing the educational materials to oncologists' offices and clinics.

One of the primary barriers to testing is the fear of waiting to begin treatment while awaiting test results. Oncologists and consumer audiences will be informed that the time lapse between testing and receiving results is currently about two weeks and is dropping rapidly as efforts to shorten the waiting time even further are being pursued. At some point, it is likely the wait time will be reduced to the point it is no longer a barrier. In the meantime, educational materials will address the concerns about delaying treatment by communicating that patients who are tested and receive treatment based on test results have better outcomes even when treatment initiation is delayed. Patient members of the LCI will consult with the task force during the development of the consumer kit, and will be made available for speaking and media engagements. They will be media trained to deliver compelling, clear, and motivating information about EGFR testing. Because family members and caregivers often push oncologists to begin treatment immediately, they are an important part of the target audience for these outreach efforts.

The LCI already urges the patients that contact them to go to oncologists working at academic medical centers or cancer centers to have molecular testing done and to have their initial treatment plan developed. Patients can be treated there or opt to take the treatment plan to their local community oncologist. This approach will continue and expand through additional educational

outreach activities on the LCI website, health fairs, and talks done at community organizations in North Carolina (i.e. Rotary Club).

Creating Short-Term Wins

Short-term wins generate momentum toward achieving the overarching objectives of the task force. It is likely it will be easier to influence change in behavior in community oncologists who already test some of their patients than those who do not perform any tests. One of the quickest and easiest ways of learning about physician practice habits is through face-to-face discussions they have with pharmaceutical sales representatives and MSLs. The task force members from pharmaceutical companies will work with their sales representatives and MSLs in North Carolina to identify community oncologists who test and those who do not. When the list is complete, the companies will use materials in the professional kit or other materials based on the contents to educate community oncologists about the importance and value of molecular testing, focusing first on oncologists who already test some of their patients.

Building on the Change

In addition to making physician calls, sales representatives and MSLs will invite thought leaders and community oncologists who routinely perform molecular testing to be speakers at educational events (e.g. Grand Rounds, symposia, teleconferences) with their colleagues. The interviews and literature point out the power of peer-to-peer influence in motivating physicians to change their behavior. Speakers will reinforce the core messaging using materials provided in the kit. Samples of patient materials will be made available to attendees who can bulk order them from sales representatives for office use.

Anchoring Change in the Culture

This step generally applies to changing the culture of an organization or company. Community oncologists may be members of professional organizations but, in truth, their connections with peers are mostly informal and based on the fact they all treat patients with

cancer. Influencing change is difficult even in well-established organizations; influencing cultural change in a loosely knit group of individuals is even more difficult (Kotter, 1996). Reflexive testing is a way of institutionalizing molecular testing without requiring cultural change. Pathologists and managers of hospital labs can institute protocols for performing molecular testing of lung cancer biopsies with certain characteristics. Reflexive testing ensures every eligible tumor sample is tested when a biopsy is done, eliminating the need for individual oncologists to order molecular testing.

Table 5 - Summary of Recommendations

Action Step	Recommendation
Creating a sense of urgency	Share results of research with professional and advocacy organizations, and pharmaceutical companies in NC. Identify target audiences.
Forming a powerful coalition	Establish a task force.
Creating a vision for change	Task force develops vision and mission statements, and objectives.
Communicating the vision	Task force develops a comprehensive communications plan, including two turnkey kits – one for healthcare professionals and one for consumer audiences.
Overcoming obstacles	Execute audience-specific tactics to motivate change. Create professional and consumer education kits.
Creating short-term wins	Focus first on community oncologists who already test some patients.
Building on the change	Leverage the power of peer-to-peer influence.
Anchoring change in the culture	Focus on increasing development of institutional protocols for reflexive molecular testing.

Influence Map

The diagram below shows the relationships between influencers and target audiences. Each audience is color coded with corresponding colored arrows showing the direction of influence. In many cases, there are multiple influences on important audiences increasing the reach and frequency of messaging and the potential for change (Keller).

Figure 11 - Influence Map

Publication and Dissemination of Research and Pilot Results

Concurrent with convening the task force, developing the communications plan, and executing tactics, I will pursue poster and plenary presentation opportunities at regional and national meetings of the American Society of Clinical Oncologists, and the Oncology Nursing Society. I will also be working with Dr. Weiss on developing and submitting a manuscript with the results of my dissertation research to peer-reviewed oncology journals for publication. Once the North Carolina pilot is complete, a separate manuscript will be prepared and submitted to journals for publication.

Expansion Planning

As mentioned, each tactic executed during the pilot will be evaluated based on pre-set criteria. One of ongoing the goals of the task force will be expanding the reach of tactics that most successfully increased the use of EGFR testing in North Carolina to regional and national audiences. Before the expansion can begin, the task force must raise enough money to fund the outreach effort. Having tangible results from the pilot demonstrating the positive impact of the tactics selected for expansion will bolster the task force's request for additional financial support. Pharmaceutical companies and molecular test manufacturers, along with other donors, will be asked to contribute money for the expansion efforts.

Identifying the best professional and consumer organization partners is another essential step in expansion planning. Task force members will compile a list of potential partners based on the ease of working with the various state-level organizations participating in the pilot and their individual experience working with partners on other initiatives. Task force members will take advantage of existing relationships with leaders of regional and national level organizations to get buy-in and support, and will ask colleagues for help gaining access to other organizations.

The task force will set new objectives for each expanded tactic and will monitor progress toward achievement of objectives on a quarterly basis. Under-performing tactics will be discontinued as quickly as possible to avoid expending resources on tactics not producing desired results.

Conclusion

This dissertation was groundbreaking; it provided the first real glimpse into the facilitators and barriers motivating community oncologists' decisions about using EGFR testing. As the knowledge about the genetic basis of lung cancer evolves, more genetic mutations have been discovered that predict the likelihood a patient will respond to specific targeted therapies. Each incremental change in the knowledge about lung cancer genetics brings more challenges

but, more importantly, it increases oncologists' ability to further personalize treatment and improve health outcomes for patients with late stage NSCLC. Laboratory testing manufacturers are developing and testing multiplex panels that screen for a number of these mutations, including EGFR; adoption of multiplex tests is likely to mirror that of EGFR testing. Therefore, I will recommend that the task force focus on educating and communicating about the complete array of molecular tests available for lung cancer patients.

APPENDIX A – LITERATURE REVIEW

Part 1: Understanding Non-Small Cell Lung Cancer and Treatments

Lung Cancer Facts and Figures

It is estimated that over 228,000 individuals in the U.S. will be diagnosed with NSCLC in 2013 (American Cancer Society, 2013) and more than 180,000 of them will have advanced or metastatic disease at the time of diagnosis. Although lung cancer accounts for only 15% of all cancer diagnoses each year, it accounts for approximately 28% of cancer-related deaths (American Cancer Society, 2013; Silvestri G. A., 2005).

NSCLC is "staged" according to the severity or extent of disease (National Cancer Institute, 2010). Staging is based on tumor size and extent of cancer spread to other parts of the body (metastasis). There are seven stages of NSCLC ranging from occult (hidden) to stage IV (metastatic) (National Cancer Institute, 2010; WebMD, 2005). Stages II, III, and IV are subdivided into A and B depending of the size and location of the tumor(s). Cancer staging is complex and is determined by tissue and blood analysis, diagnostic tests, and imaging; treatment approaches vary by cancer stage (National Cancer Institute, 2012).

Patients with stage I and II NSCLC are potentially curable (also known as operable or resectable) (Maghfoor, 2010) with surgery, radiation, laser treatment, chemotherapy, a targeted therapy or a combination of two or more of these approaches (American Cancer Society, 2013; Giaccone G. , 2007; Maghfoor, 2010). Approximately 50% of early-stage patients will be alive five years after diagnosis. NSCLC is classified as IIIB if there are malignant cells in the fluid in the space between the layers of tissue lining the lung and stage IV if the cancer has spread to the other lung or another part of the body. Life expectancy for patients with stage IIIB or IV is less than one year. As noted, most patients diagnosed with NSCLC are in advanced stages IIIB or IV, meaning the cancer has spread beyond the initial tumor site and is considered incurable.

Patients with advanced stage NSCLC cancer have a median survival of eight to ten months and overall survival of 30% at one year when they are treated with standard chemotherapy (Sequist L. B., 2007). Patients who do not respond to initial (first-line) chemotherapy treatment live an average of four to five months after diagnosis and only 11% live longer than one year. Patients who go on to receive second-line chemotherapy after failure of first-line therapy or progression after completion of treatment live an average of seven months after they are diagnosed. Less than 5% of patients with advanced disease are alive at 5 years (Tan W. W., 2011). Only a small percentage of the patients who survive two different rounds of treatment go on to receive third-line treatment. There are also several different cell types in lung cancer. Adenocarcinoma, which originates from cells lining the tiny air sacs (alveoli) in the lungs, is the most common lung cancer cell type accounting for 35% to 40% of all NSCLC cases. Cell type is an important consideration when selecting a cancer treatment because the mechanisms of cancer growth and spread vary by cell type; various cancer cell types require different treatment approaches.

Traditional Chemotherapy Treatment for Advanced NSCLC

Treatments for advanced and metastatic NSCLC are aimed at increasing time to cancer progression (progression-free survival or PFS); decreasing tumor size; preserving quality of life and performance status (ability to perform activities of daily living); delaying or decreasing symptoms, such as shortness of breath; delaying the spread of cancer cells to other locations in the body, including the brain and bones; and prolonging survival (American Cancer Society, 2010; Conaway, 2010; National Cancer Institute, 2011; Stuart, 1999).

First-line treatment. Chemotherapy is the standard first-line treatment for advanced NSCLC (Gazdar A. , 2010; National Comprehensive Cancer Network, 2012); it is given as a single drug or multi-drug combination and is usually administered by intravenous infusion in a hospital, oncology clinic, or oncologist's office. First-line treatment with platinum-based

chemotherapy medications is considered the standard of care for patients with advanced or metastatic NSCLC (Gridelli C. M., 2009; National Comprehensive Cancer Network, 2012). Most chemotherapy medications kill normal cells along with cancer cells, and are associated with significant adverse drug-related effects (Ardizzoni, 1999; De Marinis, 2008; Grossi, 2009; Wisnivesky, 2011).

The high mortality rate in advanced lung cancer is due primarily to the early spread of disease and development of resistance to therapy (Uramoto, 2007). No treatment is universally effective for treating patients with advanced NCSLC cancer. NSCLC is only moderately sensitive to chemotherapy (Maghfoor, 2010). In most cases, traditional chemotherapy provides a temporary respite from cancer progression (Gazdar A. , 2010). Approximately one-third of patients with advanced or metastatic NSCLC have an observable response to standard chemotherapy regimens and another 20% have temporary disease stabilization (Cataldo, 2011; Gridelli C. M., 2009). The majority of responses tend to be brief with a median time to cancer progression of between three to five months. Most patients relapse soon after completion of treatment and almost 50% percent of patients will be too ill to receive second-line therapy because of their rapidly progressing disease (Herbst, 2007; Shepard F. A., 2005; Wang, 2012).

Second-line treatment. Second-line therapy is the treatment given after a patient's cancer has progressed during or after first-line treatment. The goals of second-line treatment are amelioration of symptoms, and improvements in quality of life and survival; however, the impact of treatment is usually modest (Di Maio, 2010). Second-line treatment typically consists of a single chemotherapy drug not used as part of the patient's initial treatment (Maione, 2010).

Patients who derive objective benefit from first-line treatment are more likely than those who do not to benefit from second-line treatment (Di Maio, 2010). Unfortunately, many patients with advanced or metastatic NSCLC who receive second-line treatment are near the end of life. A retrospective review of patients treated in community settings revealed that more than fifty

present of lung cancer patients received chemotherapy in the last month of life, and one in five received treatment in the two weeks preceding their death. Data shows that after failure of second-line treatment, patients rarely receive any survival benefit from added therapy and they often suffer significant side effects in their final days (Di Maio, 2010; Gawande, 2010).Oncologists know a majority of their patients with advanced NSCLC are going to die within a year of diagnosis (Gawande, 2010); however, over forty percent admit to offering treatments that are unlikely to work. This is partly due to demands made by patients and their families for additional treatment and the fact many oncologists, wishing to avoid conflict or loss of hope, acquiesce (Hurst, 2005). Oncologists tend to worry more about being overly pessimistic than being overly optimistic (Gawande, 2010). It is difficult for everyone involved—patients, families, and physicians--to admit the fight is over. Hope remains as long as there are treatments that have not yet been tried. The Internet abounds with media reports of potent new cancer treatments and anecdotes of miracle cures, which helps explain the interest patients and families have in therapies regardless of their odds of helping, and physicians' willingness to go along even in the face of evidence that further treatment is futile (Di Maio, 2010; Hurst, 2005).

Recognizing the Limitations of Traditional Treatments for Advanced NSCLC

Conventional chemotherapy has improved little in terms of effectiveness in the past three decades despite the best efforts of researchers and clinicians to discover new, more effective therapies (Breathnach, 2001; Maione, 2010). One-year mortality rates increased only slightly from 35% in the late 1970s to 41% in 2004 (Huff, 2010; Printz, 2010). According to Nathan Pennell, MD, PhD, a lung cancer specialist and assistant professor of medicine at the Cleveland Clinic Taussig Cancer Center, "'We've really exhausted the capacity of traditional cytotoxic chemotherapy to make a huge difference,' he says, 'by and large, we've been trying to shift gears and go to a more targeted approach as our understanding of lung cancer changes'." (Huff, 2010).

Shifting the Treatment Paradigm to More Personalized Treatment of NSCLC

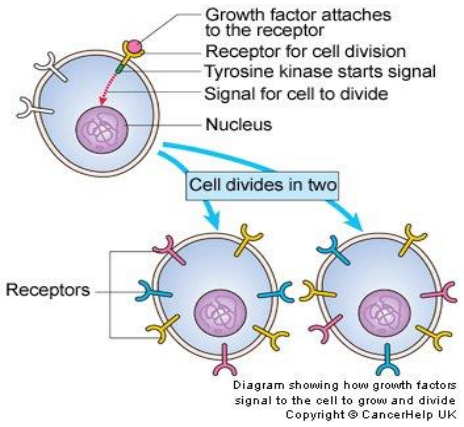
Cancer biology and genetics have advanced significantly in the past 30 years as researchers have focused attention on understanding the mechanisms of cancer development on a cellular level; they have discovered NSCLC is a heterogeneous disease with distinct genetic characteristics requiring a range of treatment options instead of the traditional one-size-fits-all approach (Huff, 2010; Pennell, 2010; Printz, 2010).

In 1986, Stanley Cohen, Ph.D., of Vanderbilt University, and Rita Levi-Montralcini, MD, an Italian developmental biologist were awarded the Nobel Prize in Physiology or Medicine for their understanding of the mechanisms of cell and organ growth, including epidermal growth factor (EGF) (Nobelprize.org, 1986). Their discovery paved the way for the development in the early 2000s of a class of anti-cancer drugs known as tyrosine kinase inhibitors (TKIs) or anti-EGFR drugs that block epidermal growth factor receptors (EGFR) in non-small cell lung cancer (Ciardiello, 2008; Dunne, 2008; Erikson, 2008; Herbst, 2007; Pennell, 2010; Printz, 2010).

The development of TKIs has led to additional discoveries that have greatly expanded the understanding of the molecular biology of NSCLC, allowing physicians to begin personalizing lung cancer treatment based on the molecular characteristics of a patient's tumor (Sequist L. V., 2008).

EGFRs or epidermal growth factor receptors are found in the cell membrane that sits between the inside and outside of a cell (Sequist L. B., 2007). The defect occurs in a region inside the cell known as the tyrosine kinase domain (Pennell, 2010). When tyrosine kinase (TK), a protein inside of a cell, binds to the tyrosine kinase receptor it triggers a process that encourages the uncontrolled cell growth and proliferation characteristic of aggressive metastatic cancer.

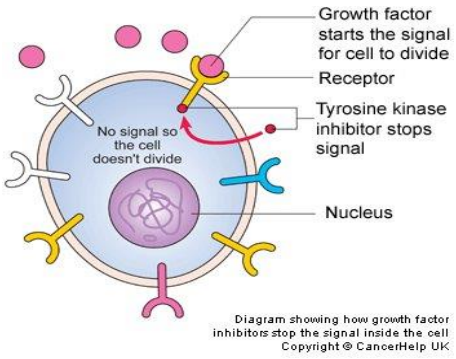
Figure 12 - Tyrosine Kinase Stimulates Cell Division and Proliferation



(Cancer Research UK, 2012)

It takes only a small amount of growth factor to stimulate lung cancer cells to proliferate in patients who have mutations in the tyrosine kinase domain of the EGFR gene; when the EGFR signal stimulating cell growth is blocked by a targeted medication cancer cells begin to die (Pennell, 2010). The presence of EGFR mutations identify a subgroup of patients with NSCLC whose tumors are "addicted" to EGFR signaling, which makes their tumors much more susceptible to treatment with tyrosine kinase inhibitors (Sequist L. V., 2008).

Figure 13 - Mechanism of Action of Tyrosine Kinase Inhibitors



(Cancer Research UK, 2012)

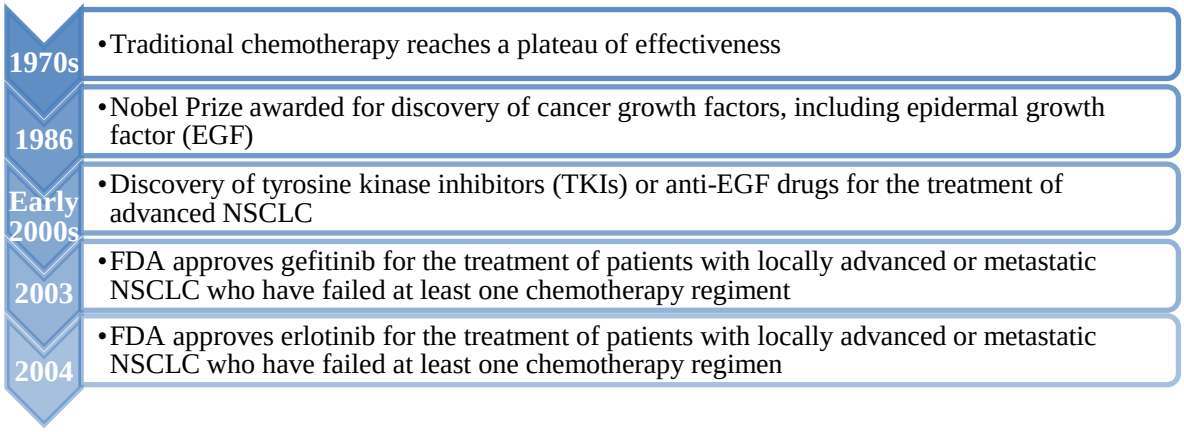
Targeted Oral Treatments for NSCLC

Tyrosine kinase inhibitors interfere with cancer cells on a molecular level, as described above, leaving normal cells untouched, unlike traditional chemotherapy that kills both cancer

cells and healthy cells, which leads to serious and potentially life threatening side effects. The FDA has approved two targeted oral TKI therapies for the treatment of advanced and metastatic NSCLC, including gefitinib (brand name Iressa™) in May 2003 (AstraZeneca, 2003) and erlotinib (brand name Tarceva®) in November 2004 (Genentech and (osi) oncology, 2011). In 2010, the FDA expanded the use of erlotinib to include maintenance treatment of patients with advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of a specific type of first-line chemotherapy. In May 2013, the FDA granted approval for expanded use of erlotinib as a first-line treatment for patients with metastatic NSCLC who test positive EGFR mutations based on results of a companion diagnostic EGFR test approved at the same time (FDA, 2013).

Although the FDA grants companies the right to market approved drugs for specific uses, physicians have the freedom to prescribe any marketed drug for any patient based on their professional judgment.

Figure 14 - Progress to More Personalized Lung Cancer Treatment



Gefitinib and erlotinib are similar chemically and were both approved by the FDA for second-line treatment; however, gefitinib's use was subsequently limited by the FDA to a small subset of patients after a study showed the drug had no impact on survival or disease-related symptoms. There has never been a head-to-head study comparing gefitinib and erlotinib; however,

experts have analyzed a number of independent studies and have concluded that gefitinib and erlotinib have comparable benefits (Keedy V. L., 2011); therefore, clinicians believe studies done with gefitinib are a reliable proxy for erlotinib. Because of the limitations placed on the prescribing of gefitinib in the US, this paper will focus on erlotinib.

Treatment with Erlotinib

The FDA based their approval of erlotinib on results from a single randomized, double blind, placebo-controlled trial of 731 patients with locally advanced (stage IIIB) or metastatic NSCLC (stage IV) who had failed at least one chemotherapy regimen (Shepard F. A., 2005; Tsao M. S.-R., 2005). The response rate with erlotinib was 8.9% compared with less than 1% response ($P < 0.001$) in the placebo group; the median duration of response was 7.9 months and 3.7 months, respectively. Rates of complete response (disappearance of all signs of cancer) and partial response (decrease in tumor size or extent of cancer in the body) in the erlotinib group were 0.7% and 8.2%. No patients in the placebo group achieved complete response and less than 1% achieved partial response. Median progression-free survival (PFS) (period of no further tumor growth or spread) was 2.2 months with erlotinib treatment and 1.8 months with placebo ($P < 0.001$). Overall survival in patients receiving active treatment was two months longer (6.7 months vs. 4.7 months, $p< 0.001$) than placebo, which was a statistically significant difference.

During the analysis of placebo-controlled clinical trials, certain patterns emerged with respect to therapeutic response to erlotinib therapy (Lynch, 2004; Paez, 2004; Pao W. M., 2004; Shepard F. A., 2005; Shepard F. A., 2005; Tsao M. S.-R., 2005). Certain clinical and demographic characteristics were associated with a higher likelihood of clinical response to erlotinib, including female gender, Asian origin, never smoking or light former smoking, adenocarcinoma tumor histology, and presence of specific EGFR mutations in tumor tissue. The first three factors listed are phenotypic characteristics that are easily identifiable by observation or simple questioning. They are used by many oncologists to guide treatment decisions even though published data shows reliance on non-genetic factors is not enough to accurately predict response

to oral TKI treatment (Cataldo, 2011; Gazdar A. , 2010; Lennes, 2011; Maione, 2010; Printz, 2010; Shepard F. A., 2011; West J. H., 2010; West J. H., 2010). On the other hand, a biopsy, which is an invasive procedure, is required to determine tumor histology (adenocarcinoma) and EGFR mutation status, which may influence oncologists to rely on easily observable characteristics when making treatment decisions.

In April 2010, the FDA approved the expanded use of erlotinib for maintenance treatment for patients with advanced or metastatic NSCLC (Genentech, 2010). The purpose of maintenance therapy is to provide continuing treatment for patients who respond or have stable disease after initial chemotherapy, which allows for continuing anti-cancer treatment before the cancer has a chance to worsen or spread further. The maintenance indication was approved based on results of the SATURN trial, which was an international, randomized, double blind, placebo-controlled study of 889 patients with advanced NSCLC. In this trial, erlotinib when used immediately after first-line chemotherapy extended overall the survival (OS) of patients by one month (Genentech, Astellas). Time to cancer progression (PFS) was 2.6 months for patients treated with placebo compared with 2.8 months for patient treated with erlotinib.

National news outlets, along with health care professional and patient web sites and blogs, carried the news of the FDA approval for the maintenance indication. Much of the coverage originated from the pharmaceutical manufacturers' press release, which implied, through use of selective statistics, that maintenance treatment with erlotinib leads to major improvements in overall and progression-free survival (Genentech, 2010).

In May 2013, the FDA approved erlotinib for use as first-line treatment of patients with metastatic NSCLC who have tested positive for certain EGFR mutations (FDA, 2013). Several prospective studies conducted with patients treated with erlotinib or gefitinib first-line after testing positive for an EGFR mutation resulted in significantly better outcomes--with objective response rates of 50% or more--as compared with response rates (< 10%) achieved in studies involving "unselected" patients who had not been EGFR tested prior to being treated; these studies further

demonstrate the utility and benefit of using pretreatment testing to determine the likelihood of response to erlotinib.

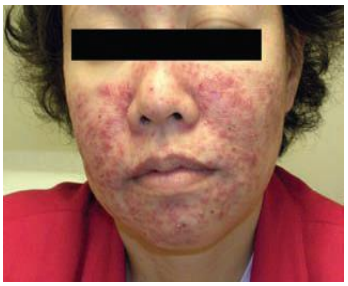
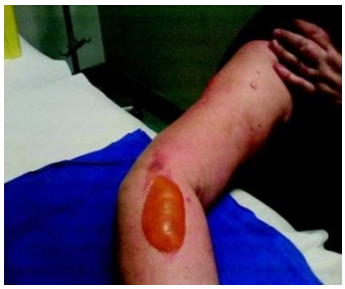
A major drawback of treating patients with erlotinib is the cost of the medication. A single month's supply of erlotinib tablets at a standard dose of 150mg each day is over $5,500, and it may or may not be covered by insurance (Drugstore.com) . Even individuals who have prescription drug coverage may face very large out-of-pocket expenses due to high copayment requirements set by some payers. Medicare Part D covers erlotinib; however, due to the coverage gap or "donut hole," seniors without supplemental insurance will incur significant costs in the first month of treatment. In fact, out-of-pocket costs for erlotinib for patients *with* insurance coverage will usually exceed patient costs associated with physician-administered chemotherapy treatments even though one treatment with standard chemotherapy is (in most cases) significantly more expensive than a one-month supply of erlotinib.

Even though the adverse effects of erlotinib are generally less serious and debilitating than those associated with traditional chemotherapy, the drug is not without side effects, which range from bothersome to deadly (Bonomi, 2007; Cataldo, 2011; Dancey, 2007; Silvestri G. A., 2005). A sizable portion of clinical trial participants treated with erlotinib experienced side effects (Dunne, 2008; Genentech and (osi) oncology, 2011). The most frequently occurring reactions included rash (49.2%), diarrhea (20.3%), anorexia (9.2%), and fatigue (9%). Almost 20% of patients required dose reductions, treatment interruptions, or discontinuation because of drug-related adverse effects compared with 2% of patients treated with placebo (Shepard F. A., 2005). Five percent of patients taking erlotinib discontinued treatment altogether due to drug-related toxicities compared with 2% of patients receiving placebo.

Rash would seem to many to be a relatively benign side effect and a small price to pay to delay cancer progression; however, many patients are unable to tolerate the uncomfortable, itchy, unsightly, and potentially disfiguring rash, which manifests as severe acne-like symptoms and skin

shedding on the scalp, face, and torso (Dunne, 2008; Genentech and (osi) oncology, 2011). In rare cases, deaths have resulted from severe rash. For many patients, rash is the most distressing part of taking erlotinib and there is often little that can be done to provide effective symptom relief. An estimated 60% to 80% of patients in the general population of patients with advanced or metastatic NSCLC taking erlotinib (outside of clinical trials) experience rash; it is one of the most common reasons for dose reductions and treatment discontinuation.

Figure 15 - Examples of Skin Reactions Caused by Erlotinib

 (Genentech, 2010)  (Oteria, 2009)

In addition to rash, eye problems occur in about one-third of patients treated with erlotinib (Dunne, 2008; Genentech and (osi) oncology, 2011). Eye-related problems include swelling, redness, itching, tear dysfunction, crusting along the lash line, and abnormal growth and thickening of eyelashes. Corneal perforation and ulceration caused by eyelash changes can be serious and result in severe pain and sensitivity to light.

Xerosis (dry skin), primarily of the arms and legs affects over one-third of patients being treated with erlotinib (Dunne, 2008); extreme dryness can result in extremely painful deep fissuring of the skin of the fingers and toes that makes it difficult to perform activities of daily living and interferes with sleep. Changes in hair growth, loss, and texture, and brittle and loose nails are also common but are easier to cope with than an overt rash or skin fissures.

Diarrhea is more common with erlotinib than traditional chemotherapy; it occurs in up to 75% of patients treated outside of a clinical trial setting. It can be severe and difficult to manage in some patients and can lead to dose reductions or treatment discontinuation.

The side effects mentioned above would seem trivial to most people who are not in a position to experience them first hand; however, they can significantly affect a patient's physical and emotional well-being, which can lead to social isolation and depression. Side effects can interfere with a patient's willingness to take medication as prescribed leading to suboptimal dosing and treatment outcomes.

One of the most serious adverse effects associated with erlotinib therapy is interstitial lung disease (ILD), which can cause progressive scarring of lung tissue that affects the ability to breathe and maintain adequate oxygen levels. It is very rare, occurring in slightly less than one percent of patients (Genentech and (osi) oncology, 2011); however, ILD is usually non-reversible and can be fatal. Other potentially deadly side effects include liver toxicity and renal (kidney) failure (FDA, 2009; Genentech and (osi) oncology, 2011; Witt, 2008).

Predicting Responders and Non-Responders to Erlotinib

The low response rate to erlotinib, high cost of treatment, adverse effects ranging from annoying to potentially fatal, and the negative consequences of prescribing a tyrosine kinase inhibitor to a non-responder suggest it is important—if not clinically imperative--to prospectively identify patients who are likely to benefit from treatment, which can be done through the use of molecular testing.

There are four basic types of molecular markers or test types including diagnostic, prognostic, predictive, and companion diagnostic (Febbo, 2011). Diagnostic markers can confirm the presence of a specific disease or classify a disease subtype (e.g. presence or absence of a specific gene mutation) based on tests done on tissue or fluids taken from a patient. Prognostic factors predict clinical outcomes (e.g. overall survival) regardless of treatment rendered. Predictive markers help clinicians choose from among available treatment options based on their likelihood of being successful in a given patient. A predictive molecular test can confirm the presence of an EGFR mutation; it is currently the most reliable predictor of a positive clinical

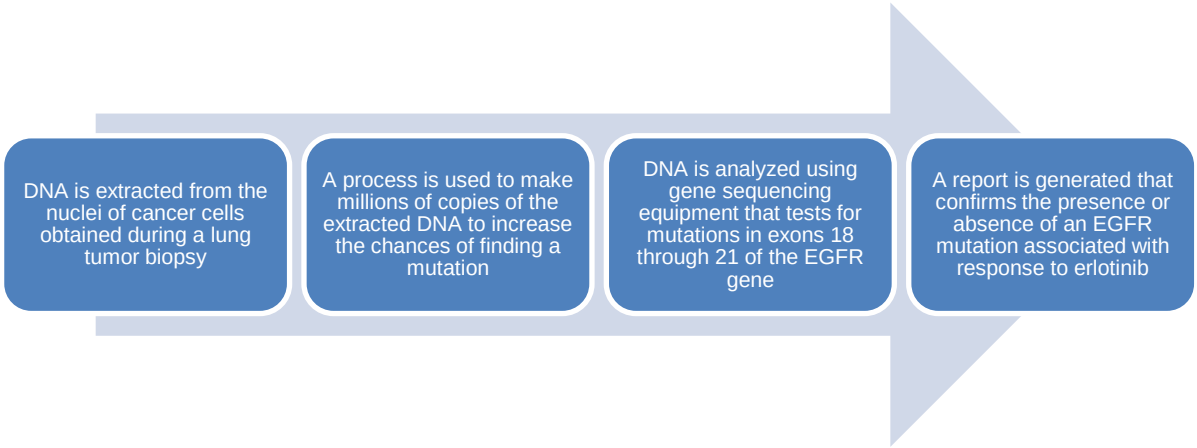
response to erlotinib (Cataldo, 2011; Gazdar A. , 2010; Printz, 2010; Shepard F. A., 2011; West J. H., 2010; West J. H., 2010). Companion diagnostic tests can be diagnostic, prognostic, or predictive; they are useful for identifying patients with characteristics associated with positive treatment outcomes.

When a physician suspects a patient has lung cancer based on imaging studies (e.g. x-ray, CT scan), a tumor biopsy (tissue sample) is usually obtained to determine if the tumor is malignant. If it is, the tumor cell type (e.g. adenocarcinoma) is identified by viewing cells under a microscope. The biopsy tissue can also undergo molecular testing to determine the presence of an EGFR mutation.

A biopsy involves obtaining a sample of the tumor by inserting a needle through the chest wall and into the tumor or fluid surrounding the lung (AstraZeneca; Printz, 2010). It is an invasive process carrying significant risk. Molecular testing is not an option for patients who do not undergo a biopsy or in cases when the tissue volume taken during a biopsy is insufficient for performing mutation analysis.

EGFR molecular testing analyzes the DNA in the EGFR gene located in tumor cells to detect genetic mutations. Known mutations, which sensitize tumor cells to the effects of erlotinib are found in four exons of the EGFR gene from exon 19 to 21 (Amler, 2005; Han, 2006; Jackman, 2009; John, 2009; Sequist L. V., 2008; Tsao M. S.-R., 2005; Yamamoto, 2008); these mutations are associated with a positive clinical response to drug therapy. An exon is a segment of a gene that contains the code for synthesis of a specific protein, such as tyrosine kinase (America Heritage Science Dictionary, 2005). Mutations in exons 19 and 21 of the EGFR gene account for 90% of all mutations associated with clinical response to tyrosine kinase inhibitors, including erlotinib (Sharma, 2007). The specificity of these tests is 100% (Kamel-Reid, 2012) with a sensitivity of 95% (Angulo, 2012). Tests yield a “yes” or “no” answer, which means an EGFR mutation is or is not present (Gochenhauer, 2012); this makes it easy for oncologists to understand the test results.

Figure 16 - Basic Steps in EGFR Mutation Testing



As with every medical proceedure, there are challenges associated with using molecular testing, including costs of $800 or more for the test and analysis (Association for Value-Based Cancer Care, 2012; Levenson, 2008); the need to use tissue extracted during a biopsy instead of a simple blood test (Association for Value-Based Cancer Care, 2012; Printz, 2010; West J. H., 2010); the lack of consistent regulatory standards; inconsistency in oversight across laboratories performing the tests; lack of definitive evidence that routine testing of all advanced NSCLC patients increases overall survival, the risks associated an invasive procedure (biopsy) (West J. H., 2010); and a delay of 5 to 7 days or longer to receive test results, which could delay the initiation of treatment. However, it is not known at this time if or how often these factors play a role in an oncologist's decision to forego pretreatment molecular testing.

Despite these challenges, Dr. Mark Kris, a world-renown expert in lung cancer, is a staunch advocate of pretreatment molecular testing (Association for Value-Based Cancer Care, 2012; National Lung Cancer Partnership, 2012); he believes genetic testing for EGFR mutations in advanced lung cancer patients is and should be driving treatment decisions. He has based his opinion on the results of the IPASS (Iressa Pan-Asian Study) and the TORCH (international multicenter randomized phase III study of first-line erlotinib followed by second-line cisplatin plus gemcitabine

versus first-line followed by second-line erlotinib in advanced non-small cell lung cancer) studies. The TORCH study is reviewed in the next section.

IPASS was a landmark study that conclusively demonstrated that molecular testing is a superior method of identifying patients appropriate for TKI-based treatment as compared with the use of clinical characteristics or observations (Gridelli C. B., 2008). All subjects were Asian, had advanced or metastatic adenocarcinoma NSCLC, were either non-smokers or light former smokers, and had no prior cancer treatment; they all underwent molecular testing prior to starting treatment. Sixty percent of the participants tested positive for EGFR mutations. The remaining 40% of subjects had clinical or demographic characteristics consistent with response to erlotinib or gefitinib, but they did not have an EGFR mutation.

Patients in the study were randomized to receive gefitinib or standard first-line combination chemotherapy. The patients who tested positive for EGFR mutation and treated with gefitinib experienced significantly higher response rates and progression-free survival than similar patients treated with chemotherapy. The 40% of study participants who did not have an EGFR mutation had a significantly better response rates and progression-free survival with standard chemotherapy than similar patients treated with gefitinib. This study demonstrated clearly that using clinical characteristics to make treatment decisions could result in overprescribing of erlotinib to patients who would have better outcomes if treated with standard chemotherapy.

Although a growing body of published research confirms the benefits of prospective molecular screening of patients with advanced NSCLC, many oncologists continue treating every patient the same, as if NSCLC is a homogeneous disease (Gridelli C. B., 2008). Oncologists who understand individual patients may respond differently to erlotinib most often use clinical characteristics to identify the patients they think are likely to respond instead of ordering EGFR tests.

In fairness to oncologists who do not order EGFR tests for their patients with advanced NSCLC, the FDA does not require molecular testing be done as a condition of prescribing erlotinib.

However, the two most prominent professional organizations that produce guidelines for cancer treatment—the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN)--recommend testing, especially for patients being considered for first-line treatment with a TKI (American Society of Clinical Oncology, 2011; National Comprehensive Cancer Network, 2012).

ASCO, the world's largest professional organization of oncologists, in 2011 issued a preliminary clinical opinion based on the outcome of five randomized, controlled trials, recommending that patients with advanced or metastatic NSCLC undergo EGFR mutation testing to determine the most appropriate first-line therapy (Keedy V. L., 2011).

Also in 2011, the NCCN, an alliance of 21 leading cancer institutions in the U.S., issued a clinical management guideline recommending EGFR testing be done after a tumor has undergone tumor cell-type (histologic) analysis and has been determined to be an adenocarcinoma before deciding on a treatment approach (National Comprehensive Cancer Network, 2012). NCCN also recommends patients with advanced or metastatic NSCLC who test positive for EGFR mutation at the time of diagnosis receive erlotinib first-line and patients with unknown or negative EGFR mutation status be treated with conventional chemotherapy even when patients have clinical characteristics suggestive of response to erlotinib, such as female gender, non-smoking history, and Asian race.

The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society have also gone on record as being in favor of EGFR mutation testing of patients with advanced or metastatic adenocarcinoma or non-specified NSCLC (Travis, 2011). These groups collectively concluded that EGFR mutation is a validated predictor of response and progression-free survival in advanced or metastatic lung cancer patients treated with erlotinib or gefitinib.

The Consequences of Selecting the Wrong Treatment

At the time of diagnosis or when NSCLC progresses despite treatment, either immediately or after a period of "remission" (progression free survival), oncologists and their patients are faced with the question of what to do next. Treatment options include chemotherapy; erlotinib; crizotinib (brand name Xalkori®), which is a relatively new treatment that is effective in the small percent (4%) of advanced and metastatic NSCLC patients with a specific mutation in the ALK gene (Pfizer, 2012); bevicizumab (Avastin®, Genentech), a monoclonal antibody; or a combination of two or more of these treatments (Genentech, 2010; Pfizer, 2012). They can also choose to stop treatment. If the physician and/or patient are not yet ready to stop treatment, erlotinib is an easy option based on its convenience and safely profile compared with standard chemotherapy or other cancer-fighting medications given by intravenous infusion.

However, the results of recent studies indicate the order of treatment—standard chemotherapy given as first-line followed by erlotinib second-line or vice versa--matters greatly with respect to treatment outcomes (Gandara, 2010; Gridelli C. B., 2008; Lennes, 2011; Printz, 2010; West J. H., 2010; West J. H., 2010; West J. H., 2010). People who have an EGFR mutation making their lung cancer more susceptible to erlotinib fare significantly better when treated with the erlotinib first instead of chemotherapy; the opposite is true for people who lack the mutation(s) predictive of a positive clinical response to oral TKIs.

In the TORCH study, patients with advanced or metastatic NSCLC were randomly assigned to receive first-line treatment with chemotherapy or erlotinib followed by cross-over to the other treatment at the time of cancer progression (Brooks, 2012; Gandara, 2010; Gridelli C. B., 2008; West J. H., 2010). Only 55% of patients who started on chemotherapy went on to receive erlotinib and fewer than half (49%) of those started on erlotinib crossed-over to chemotherapy because they were too sick to receive more treatment.

The results of the planned interim analysis showed the outcomes of patients who received erlotinib first-line were 40% worse than those who received chemotherapy first and the study was stopped for safety reasons. Patients who received chemotherapy first-line had a 28% response rate vs. those who received it second-line (10%) after erlotinib. The researchers predicted the response rates would be similar in the two groups and patients who received erlotinib first could be switched to chemotherapy and achieve the same outcome they would have if treated with chemotherapy first, which was not the case. This study made it clear that starting unselected patients on erlotinib instead of chemotherapy has serious health and mortality consequences, in addition to financial costs associated with purchasing ineffective treatment and unnecessary exposure to adverse drug events. The opposite is true as well. There is a "significant penalty in terms of overall survival" when patients with an EGFR mutation are treated with chemotherapy rather than erlotinib (West J. H., 2010). People with EGFR mutations often have a sustained period of progression free survival that is extremely unlikely to be achieved with traditional chemotherapy. They die faster when given chemotherapy instead of erlotinib.

Ongoing analyses of the results of the TORCH study have led researchers to conclude that only those patients with an EGFR mutation should be treated with erlotinib first-line (Brooks, 2012; Gandara, 2010; National Lung Cancer Partnership, 2012; West J. H., 2010; West J. H., 2010). Patients with unknown or negative EGFR status should be treated initally with chemotherapy. It is very unusual for patients who test negative for EGFR mutations to have a meaningful response to erlotinib (1.1%) (Mok, 2009). Experts believe erlotinib should be reserved in these patients until other, more traditional options have been tried because erlotinib is likely to cause more harm than good in patients lacking an EGFR mutation.

The Prevalence of EGFR Testing in the U.S.

The IPASS and TORCH trials demonstrate clearly that EGFR mutation testing is effective in identifying patients who are more likely to derive benefit from erlotinib. In light of

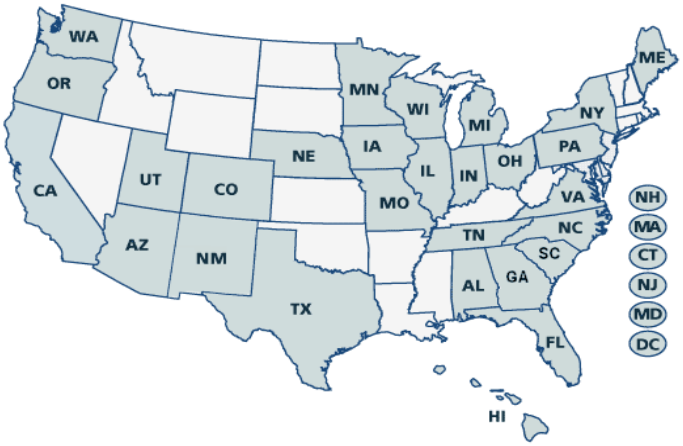
the weight of the evidence, the importance and role of EGFR testing of patients with advanced NSCLC is difficult to deny. However, evidence suggests strongly that most oncologists have not yet adopted EGFR testing as a routine part of their clinical practice.

ASCO believes molecular mutation testing use is widespread at academic medical and comprehensive cancer centers and is rarely used in community oncology practices where more than 80% of cancer patients are treated (Community Oncology Alliance, 2011; Keedy V. L., 2011). This suggests there is significant underutilization of EGFR testing in non-small cell lung cancer patients being treated in the U.S. However, the extent of the problem was unknown until late 2011.

An analysis conducted by Julie Lynch, PhD, at the University of Massachussetts, Boston, was presented at a conference sponsored by the American Association of Cancer Research (AACR) in fall 2011. The study, which was the first comprehensive analysis of the use of EGFR testing ever published, confirmed EGFR mutation testing is vastly underused by oncologists treating lung cancer patients in the US (Alt, 2011; Lynch J. A., 2013). Dr. Lynch obtained the data used in the analysis from Genzyme Corporation, which launched an EGFR diagnostic test in 2005. The data represents an estimated 98% of EGFR testing conducted by community hospitals. The analysis included only a small amount of data from the 59 National Cancer Institute (NCI) designated cancer centers, which are select academic medical centers and comprehensive cancer centers recognized for scientific excellence and their range of cancer research approaches. Most NCI designated centers have separate agreements with Genzyme or employ their own assays, so their data were not available for evaluation. Dr. Lynch merged the Genzyme database with data from the U.S. Census Bureau, the Centers for Disease Control, The National Institute of Standards and Technology, the Centers for Medicare and Medicaid Services, and the NCI to create a nationwide map showing the county-by-county use of EGFR testing.

In 2010, the over 6,000 acute care hospitals in the U.S. combined ordered 6,056 EGFR mutation tests (Alt, 2011; American Hospital Association, 2012; Lynch J. A., 2013). Independent pathology laboratories ordered an additional 527 tests, and independent outpatient oncology clinics or oncologists ordered an additional 258 tests. NCI centers ordered 1,019 of the roughly 6000 tests, which was not a complete count as noted above. As a point of reference, over 280,000 patients are diagnosed with advanced or metastatic NSCLC a year (American Cancer Society, 2013). Although reporting from NCI-designated centers was limited, a map created by Dr. Lynch revealed that testing was clustered in geographic areas surrounding NCI centers, suggesting it was likely the procedures being followed by these institutions were influencing the behavior of oncologists in surrounding communities (Alt, 2011; Lynch J. A., 2013), which leaves much of the country underserved.

Figure 17 - Location of National Cancer Institute Designated Cancer Centers



(Office of Cancer Centers, 2012)

The Lynch data showed large regional variations in the use of EGFR testing (Alt, 2011; Lynch J. A., 2013). The top states for EGFR testing were New York (1,024 tests), Florida (496), California (352), Pennsylvania (338), Massachusetts (334), Maryland (284), and Illinois (272); together, these seven states accounted for more than 50% of EGFR tests performed in 2010. States without at least one NCI-designated cancer center had extremely low testing rates. However, the presence of an NCI Cancer Center was no guarantee testing was being performed

routinely. For example, only five tests were performed in Utah, the home of the Huntsman Cancer Institute, and six were done in New Mexico, the home of the University of New Mexico Cancer Center.

EGFR tests were performed in only 357 (11%) of the 3,124 counties in the U.S. The counties accounting for the highest number of tests included Nassau County, NY; New York County, NY; Baltimore County, MD; Kent Country, MI; and Cook County, IL. Other counties with a relatively high number of tests are located in areas surrounding Phoenix, AZ, Boston, MA, Miami, FL, and Los Angeles, CA. Most of these counties have or are close to an NCI-designated cancer center. Counties with the highest incidence of lung cancer had the lowest rate of EGFR testing; these counties tended to be rural with low socioeconomic status and relatively poor access to health care.

Based on available data, the use of EGFR testing in treatment selection for patients with advanced or metastatic NSCLC is very low (Alt, 2011; Chustecka, 2013; Chustecka, 2013; Lynch J. A., 2013). Several factors may contribute to this low utilization rate. The cost of tests range from $700 to $1000 per test, but the cost is coming down rapidly as laboratories are finding ways of reducing expenses and increasing throughput. However, in comparison to the over $5,500 monthly cost for erlotinib tablets, the cost of an EGFR test seems to be a reasonable investment. There are other challenges associated with testing, such as the need for a biopsy and a 5 to 7-day waiting period for test results.

According to the Lynch data, many oncologists do not order molecular tests even though the practice is endorsed by the major organizations responsible for setting guidelines for oncology practice in the U.S and publicized widely in medical journals and other medical media. On paper, the choice seems clear, but it is obviously not or EGFR testing would be more widespread. There are obviously barriers to adoption of molecular testing based on the Lynch data, but we do not know for sure what those barriers are. There are also factors influencing and motivating oncologists to use the

tests. Part two of this literature review will focus on facilitators and barriers to adoption of medical innovation along with an analysis of the relative success of various methods used to influence physician behaviors.

Part 2: Influencing Physicians' Clinical Behaviors and Decisions

There is significant and growing interest in the medical community in the burgeoning ability to "personalize medicine" to better meet individual patient needs and circumstances, and improve quality of health care. The concept relies on an increasingly sophisticated understanding of the genetic basis of disease and response to drug therapy, which allows physicians to tilt the risk-benefit balance more strongly in favor of patient benefit by predicting which patients are more likely to gain the greatest benefit from a specific therapy while at the same time minimizing associated treatment-related risks. EGFR testing has been available in the US since 2005. However, as noted in part one of this chapter, having widespread access to molecular testing, clinical guidelines issued by prestigious oncology organizations, and recommendations from well-respected expert thought leaders has done little to motivate the majority of oncologists to perform EGFR testing before prescribing treatment for specific patients.

Why is pre-treatment EGFR testing underused? Lung cancer experts have offered their personal opinions, but there are no published data about decision criteria used by oncologists when considering whether to perform EGFR testing for their patients with advanced or metastatic NSCLC; therefore, we are left to examine facilitators and barriers associated with the uptake of innovations in other areas of medical care for clues. The research component of this project goes a step further by asking practicing oncologists about their use of EGFR testing and the criteria they use for making decisions about testing patients they care for.

Facilitators of Change in Medical Practice

Concerns about quality of health care are nothing new; however, concerns about health care spending are becoming more widespread and urgent as the federal deficit grows and health care costs become an increasing large percent of the US gross domestic product (GDP) (Centers for Medicare and Medicaid Services, 2012). Cancer medications—particularly newer targeted therapies-- are contributing significantly to rising health care costs; the affordability of cancer medications is an increasing concern for patients, providers, and payers. A recently published analysis of over 4000 health claims revealed an average health care expenditure of over $125,000 per cancer patient (The American Journal of Managed Care, 2012); the majority of costs are associated with outpatient cancer services, including medications. The cost of cancer treatments is rising at a rate of 20% per year, which is almost double the projected increase in the cost of other prescription medications (11.4%). Scrutiny is growing and the trend is considered by many to be unsustainable. Expensive targeted therapies such as erlotinib bear a large responsibility for the dramatically rising cost of cancer treatments. According to Express Scripts, a pharmacy benefit management company, the cost of oncology medications and their administration will rise to $173 billion per year in 2020 (Express Scripts Specialty Benefit Services, 2010).

A wide range of stakeholders, including patients and advocacy groups; health care professionals and their professional societies; health systems; payers ranging from private insurers to managed care organizations (MCOs) to federal and state governments and agencies; lawmakers and regulators; institutes, non-profit and voluntary organizations; and others are working on finding ways of improving cancer care quality while containing or reducing costs (Centers for Medicare and Medicaid Services, 2012; National Cancer Institute, 2012).

Although there are many barriers to widespread adoption of EGFR testing in NSCLC, there are also many levers for improving quality of cancer care, while containing costs. This section focuses on organizations and initiatives with a realistic potential of influencing

oncologists to increase their use of EGFR testing when caring for patients with advanced or metastatic NSCLC. There is also the potential for smaller scale initiatives to influence oncologists to order more EGFR tests but due to their limited scope and reach, they will not be discussed in here.

Congress and the Patient Protection and Affordable Care Act. Although there is significant interest in doing a better job of spending health care dollars to improve health care quality, efficiency, and health outcomes, the U.S. does not currently use cost effectiveness analysis to set health care priorities or evaluate health care expenditures (Farina, 2012). However, that is changing because of several new initiatives aimed at increasing health care quality and affordability.

In March 2010, Congress enacted the Patient Protection and Affordable Care Act (P. L. 111-148), which was amended in the same year by the Health Care and Education Reconciliation Act (P. L. 111-152) (Kaiser Family Foundation, 2012). The Affordable Care Act or ACA was intended to be a major driver of comprehensive health care reform in the U.S. The ACA provides significant financial help to individuals with low to moderate incomes to help them afford health care coverage; it also requires significant health insurance reforms, such as stipulating minimum covered benefits, out-of-pocket limits for covered services, elimination of lifetime benefit caps, and discrimination based on pre-existing health conditions.

The ACA has a number of provisions aimed at reducing or maintaining costs and improving the efficiency of the health care system. The accountable care organization (ACO) is one of the new health care delivery models arising from the ACA (Centers for Medicare and Medicaid Services, 2012; Greenapple, 2012). An ACO is an integrated network system of health care providers that voluntarily agrees to manage all of the health care needs for a defined population (minimum of 5,000 Medicare beneficiaries) for a specific length of time (minimum of three years) (Centers for Medicare and Medicaid Services Center for Medicare and Medicaid Innovation, 2012). Currently, there are no

quality measures associated with cancer treatment delivered by ACOs; however, this is likely to change as spending on cancer treatments continues to outpace increases in other health care costs.

Although benefits of pretreatment EGRF testing have been demonstrated clearly, it has not yet been addressed by any of the efforts aimed at reining in health care costs or improving affordability of medicines. Taking advantage of such an opportunity—which is already supported by extensive research and expert opinion-- has the potential to garner a "quick win" by helping to demonstrate the positive impact of health care reform on cancer patient care, costs, and treatment outcomes.

Comparative effectiveness research. One major area of interest in health care reform is comparative effectiveness research (CER), which evaluates the impact of different treatment options for a given condition in a specific patient population to provide evidence of effectiveness, benefits, and harms that can be used to make better informed treatment decisions (Agency for Healthcare Research and Quality, 2012). CER will generate evidence-based information allowing patients, caregivers, and clinicians to make better-informed and potentially more cost-effective health care decisions. The IPASS and TORCH studies mentioned in part one of chapter two are examples of comparative effectiveness research. The 2009 American Recovery and Reinvestment Act (ARRA) of 2009 (Pub.L. 111-5), also known as the economic stimulus package, provided $1.1 billion for translational and health services research (National Cancer Institute, 2012). The National Cancer Institute received $400 million of that money to fund cancer-related comparative effectiveness research; currently, none of these funds is being spent on improving the care of patients with lung cancer.

U.S. Department of Health and Human Services. The U.S. Department of Health and Human Services (DHHS) is the principal federal agency responsible for protecting the health of Americans and providing essential human services (U.S. Department of Health and Human Services, 2012). By virtue of their Medicare program, DHHS is the nation's largest insurer. The DHHS

collaborates with states to fund and administrate Medicaid and the State Children's Health Insurance Program (SCHIP), which assist low-income individuals to increase their access to health care services (Medicaid.gov, 2012; U.S. Department of Health and Human Services, 2012).

Twelve agencies make up DHHS, but not all have responsibility or the authority to influence the rate of adoption of EGFR testing. Those that do or may in the future include the Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control (CDC), Centers for Medicare and Medicaid (CMS), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH).

Agency for Healthcare Research and Quality. The Agency for Healthcare Research and Quality (AHRQ) has three main focus areas for improving health care delivery, including access to care and health outcomes for all Americans; encouraging adoption of evidence-based decision-making to increase the effectiveness of treatments and improve subsequent health outcomes; and improving the effectiveness of health services and reducing unnecessary costs by making the transformation of research into clinical practice more efficient (Agency for Healthcare Research and Quality, 2012; Agency for Healthcare Quality and Research, 2012). AHRQ measures success by evaluating improvements in health care in terms of enhancements in quality of life and health outcomes, reductions in morbidity and mortality, and value generated from health care expenditures.

The AHRQ Center most relevant to this paper is the Center for Outcomes and Evidence (COE). The COE encourages sustainable systemic change by working with health care providers, consumers, payers and policy makers, and motivating them to implement evidence-based practices demonstrated to improve quality of care and health outcomes; they also direct and support research on appropriate use of medications and provide evidenced-based information about medications and other treatment options. The COE has focused primarily on improving screening techniques to increase early detection and diagnosis, and providing educational information to consumers on different types

of cancer; however, this could change in the future as a result of rising concerns about the affordability and access to expensive cancer treatments.

Centers for Disease Control. The Centers for Disease Control's (CDC) Office of Public Health Genomics (OPHG) is responsible for evaluating genomic tests and promoting appropriate use of those tests (Office of Public Health Genomics, 2012). OPHG focuses primarily on promoting testing for single gene disorders, such as cystic fibrosis, fragile X syndrome, and sickle cell disease. However, they also promote the use of genomic tests to increase the probability a patient "gets the right drug at the right time." They recommend EGFR mutation analysis be performed on patients with advanced or metastatic NSCLC to prospectively predict their response to erlotinib therapy; this recommendation was based on an evidence-based systemic review of the analytic validity, clinical validity, and utility of the test in specific clinical scenarios (CDC Office of Public Health Genomics, 2012).

Centers for Medicare and Medicaid Services. The Centers for Medicare and Medicaid Services (CMS) is the largest single payer of cancer-related health care services in the U.S. (Potetz, 2009). Persons ages 65 and over make up about 13% of the U.S. population but account for slightly over half of new cancer cases and 65% of lung cancer cases. In 2004, the National Cancer Institute estimated Medicare accounted for 45% of total spending on cancer care in the U.S. In the same year, lung cancer accounted for 20% of Medicare spending on cancer (Beasley, 2012).

Medicare Part D covers erlotinib, but oncologists must apply for prior approval for individual patients before coverage goes into effect (Blue of California, 2012). Medicare recipients with supplemental drug coverage must also meet the requirements of their private insurance carriers; many of them require patients to pay a portion of the cost of their erlotinib prescriptions (Centers for Medicare and Medicaid Services, 2012).

CMS serves as a reference point for private health insurers and other payers; other payers usually follow CMS' lead when establishing their criteria for covering health care services and medications, including cancer care (Chernew, 2010; Okon, 2012). Usually changes in Medicare benefits, policies, and requirements influence health care delivery throughout the U.S. (Cassidy, 2010). CMS began covering EGFR testing in 2013, which could influence other payers follow suit (Centers for Medicare and Medicaid Services, 2012).

Medicaid, a joint federal - state partnership to provide health care to low income Americans meeting strict eligibility requirements, does not require states to provide prescription drug coverage to Medicaid recipients; however, all states currently provide coverage of outpatient prescription medications (Medicare.gov, 2012). In most cases, state Medicaid programs cover the cost of erlotinib, usually with restrictions; however, they are not required to pay for EGFR testing.

CMS Center for Medicare and Medicaid Services Innovation Center. CMS' Innovation Center was established by the ACA to foster change in the way health care is delivered and paid for by identifying, developing, supporting and evaluating innovative system-based models for health care delivery and funding for Medicare, Medicaid, and SCHIP beneficiaries (CMS Centers for Medicare and Medicaid Services Center for Medicare and Medicaid Innovation, 2012). The Center received ten billion dollars in funding for the period of 2010 through 2019 (Reid, 2010); they provide grants for innovative projects with a potential for improving the health and health care of all Americans, while reducing costs.

To date, the Innovation Center has awarded one grant that may ultimately motivate more oncologists to test patients for EGFR mutations before prescribing treatments. Innovative Oncology Business Solutions, Inc. was awarded a three-year, $20 million grant to fund the implementation and testing of the medical home concept by seven community oncology practices across the US The goal of the community oncology medical homes "COME HOME" project is to improve the appropriateness and quality of cancer care by coordinating all outpatient oncology

care including medication management for patients served by the seven participating community oncology practices located in Florida, Georgia, Maine, New Mexico, Ohio, Pennsylvania, and Tennessee. If the oncology practices adopt the practice of performing EGFR testing in patients with advanced and metastatic lung cancer, it may also motivate other practices to do so. However, it will likely take several years for the results of this project to be published and influence cancer care delivered by others.

Federal Food and Drug Administration. The Federal Food and Drug Administration (FDA) is the federal regulatory agency responsible for protecting the public's health by assuring the safety and efficacy of human medicines and medical devices (U.S. Food and Drug Administration, 2012). The FDA Center for Drug Evaluation and Research (CDER) regulates the approval of prescription medications. Another division, the FDA Center for Devices and Radiologic Health (CDRH) is responsible for evaluating the applicability and safety of genetic tests and granting approval for marketing.

In recent years, the FDA has approved a number of molecular tests to help oncologists identify patients who are more likely to respond to treatment who are more or less likely to respond to specific cancer treatments, such as erlotinib. In other cases, the FDA requires oncologists to test patients before a specific cancer therapy is prescribed.

The FDA continues to raise the bar by approving targeted therapies for use in patients with certain types of cancer who harbor genetic mutations making them more likely to respond to the specific treatment. The agency is also becoming more aggressive in approving—and in some case requiring--companion diagnostic tests be used to identify patients who are the best candidates for a specific medication based on their genetic profile. One example is the recent approval of erlotinib for first-line treatment of patients with metastatic NSCLC who test positive for specific EGFR mutations. There are now several molecular tests being used to identify patients who are more likely to respond to specific cancer medications. Even though practicing oncologists can choose in most cases to

ignore FDA guidance on testing, it is reasonable to assume increasing payer pressure and mandates aimed at reducing costs and improving health outcomes will likely increase use of pretreatment molecular testing in cancer patients.

National Institutes of Health. The National Institutes of Health (NIH) is the largest single source of health research funding in the world (National Institutes of Health, 2012; National Institutes of Health, 2012); it is comprised of 27 Institutes and Centers, each having a unique mission and research agenda. The organization's mission is to use the results of funded research to enhance health, reduce morbidity and mortality, and reduce burdens of illness and disability (National Institutes of Health, 2011). In addition to funding research and fostering collaboration between researchers and research institutions, NIH also provides web-based health and disease-related resources for the public. NIH member organizations most relevant to this paper include the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI).

National Cancer Institute of the National Institutes of Health. The National Cancer Institute's (NCI) ability to affect clinical oncology practice stems from their reputation for impartiality, credibility, and funding of basic research and clinical trials designed to translate research into practical clinical applications. NCI research is instrumental in influencing adoption of new technologies and disseminating treatment-related findings, albeit at a slow pace in many cases.

The NCI is responsible for coordinating the National Cancer Program, created in 1971 when President Nixon signed the National Cancer Act declaring "war on cancer" (Kufe, 2003), conducting and funding cancer research, training researchers and physicians, and disseminating to health care professionals and consumers information about cancer prevention, diagnosis, treatment, and control (National Cancer Institute, 2011). The NCI has 23 Offices, and 11 Advisory Boards and Groups; the two most relevant to this research, the Clinical Trials

Cooperative Group Program and the Office of Cancer Genomics are discussed in more detail below.

In 2011, NCI spent almost $300 million on lung cancer research initiatives, including over $25 million on 59 projects aimed at increasing knowledge about EGFR mutations and use of EGFR testing (National Cancer Institute; National Cancer Institute). As of February 2013, there are over ten active phase III and IV clinical trials studying the efficacy of tyrosine kinase inhibitors, including erlotinib, gefitinib and novel compounds, in the treatment of patients with advanced or metastatic NSCLC harboring certain mutations in the EGFR gene (National Cancer Institute, 2013).

In addition to funding research, the NCI also provides a wide range of educational information on their web site about specific cancers and treatments, including lung cancer (National Cancer Institute, 2013). In the health care professional information section on NSCLC treatment, erlotinib is listed as a treatment option for patients with stage IV (metastatic) NSCLC (National Cancer Institute, 2013). There is also a consumer-oriented targeted cancer therapies fact sheet mentioning erlotinib and gefitinib as treatment options for patients with metastatic NSCLC (National Cancer Institute, 2012); the fact sheet explains the way these two medications inhibit the tyrosine kinase activity of EGFR, but they do not mention molecular testing. In the health care professional section of the web site, NCI recommends oncologists perform pretreatment EGFR testing on tumors tissue taken from patients with advanced or metastatic NSCLC to help them individualize treatment based on a tumor's genetic profile and likelihood it will respond to treatment (National Cancer Institute, 2013).

The Clinical Trials Cooperative Group Program (CTCGP) is made up of than 3,000 institutions and 14,000 investigators funded by the NCI (National Cancer Institute, 2009); more than 25,000 new patients participate in group-conducted clinical trials each year. The CTCGP increases awareness of and recruitment into NCI supported clinical trials improving the speed of trial

enrollment, completion, and publication. The NCI has and is currently funding a number of clinical trials under the auspices of the CTCGP aimed at increasing the understanding and use of EGFR testing in clinical practice.

The NCI Office of Cancer Genomics (OCG) has a growing emphasis and commitment to increasing research and integration of genomics into clinical oncology practice (Patlak, 2011). The OCG aims to increase understanding of cancer at the molecular level with the goal of improving cancer care and health outcomes, and turning genomic information into therapeutic strategies for individual patients (National Cancer Institute Office of Cancer Genomics; National Cancer Institute Office of Genomic Research, 2012). They have done work in lung cancer; however, it has not been specific to non-small cell lung cancer or EGFR testing.

National Human Genome Research Institute of the National Institutes of Health. The National Human Genome Research Institute (NHRGI), originally known as the National Center for Human Genome Research (NCHGR) was founded in 1989, by the NIH, in collaboration with the U.S. Department of Energy, to fulfill the NIH's role in the International Human Genome Project (HGP) (National Human Genome Research Institute, 2012). The human genome-mapping project started in 1990 and was completed in 2000. The map served as a foundation for many important medical discoveries in the past decade, including research that has provided an increasingly sophisticated understanding of the molecular basis of lung cancer and contributed to the development of targeted cancer therapies.

The NHGRI established the Cancer Genetics Group (CGB), which is comprised of eight groups or units responsible for researching various aspects of cancer genetics; these groups are responsible for contributing to the discovery and understanding of genes associated with cancer susceptibility and progression (National Human Genome Research Institute, 2012). The Varmus Group, which is part of the CGB, is focusing on models of human cancers, particularly lung adenocarcinomas and the development of targeted therapies; the group has contributed

significantly to the understanding of the role of EGFR in development of lung cancer and development of targeted lung cancer treatments.

Institute of Medicine. The Institute of Medicine (IOM) is part of the National Academy of Sciences (Institute of Medicine, 2012). It is an independent nonprofit nongovernmental organization providing unbiased guidance and evidence on health, health care, and medicine to policymakers, decision-makers, and the public. Much of their work is at the behest of Congress, federal agencies, and independent organizations. The IOM sponsors the National Cancer Policy Forum that brings together thought leaders from the cancer community to focus on cancer policy issues (Institute of Medicine, 2012). While Forum members are interested in increasing diffusion of innovation in cancer care to enhance quality, they generally do not focus on interventions specific to particular cancers or cancer treatments.

While none of the various government initiatives reviewed here apply directly to increasing the use of pretreatment EGFR testing, they demonstrate willingness to address issues of quality and affordability of health care. Given the large amount of federal funds being allocated to cancer treatment, it is likely increasing attention and effort will be placed on influencing and motivating appropriate drug selection based on molecular technologies that can identify the most appropriate treatment(s) for individual cancer patients.

Lung Cancer Mutation Consortium and the Biomarkers Consortium. The identification of biomarkers is an essential element in the quest for more personalized medicine. The National Lung Cancer Partnership (NLCP) is a lung cancer advocacy group consisting of researchers, health care professionals, patients, and patient advocates (The Lung Cancer Mutation Consortium, 2012). The NLCP sponsors the Lung Cancer Mutation Consortium (LCMC), which is voluntary group of 16 cancer centers across the US dedicated to prospectively examining NSCLC tumors, and matching patients to the best possible therapies based on molecular testing results. The organization's primary goal is to "provide the most up-to-date care for lung cancer patients, while collecting valuable

information about the frequency and characteristics of abnormalities found in lung tumors to further improve patient care." Initial funding for the Consortium were made available to the NCI through the American Recovery and Reinvestment Act; the funding has now expired and the LCMC is raising funds from the private sector (Lung Cancer Mutation Consortium, 2012).

The Consortium began offering free EGFR mutation testing for NSCLC patients nationwide through a study being conducted by 14 of its participating clinical sites until initial funding from the federal government expired in 2011 (Lung Cancer Foundation of America, 2010; Lung Cancer Mutation Consortium, 2012). The study reopened in August 2012 using funds donated by individuals and corporations.

In addition to increasing access to EGFR testing through participating sites, LCMC has initiated a nationwide campaign aimed at health care professionals, and lung cancer patients and their families to increase awareness of the availability of EGFR testing and the critical role it plays in treatment selection.

A second group, the Biomarkers Consortium is a public-private partnership founded by the FDA, NIH, and pharmaceutical companies (Farina, 2012). The organization is seeking to accelerate the development and dissemination of technologies, medicines and therapies for treatment of disease, including cancer (Biomarkers Consortium, 2012). They are working to qualify new and existing technologies that are useful in predicting drug response or improving clinical practice, and making the results broadly available to the scientific community. Although they are focusing on developing outcome measures for lymphoma and lung cancer, their research focus does not currently include molecular testing for lung cancer (The Biomarkers Consortium, 2012).

Patient advocacy organizations. There are a number of patient advocacy groups working on improving health outcomes and access to lung cancer treatment, and reducing deaths from the disease; the Lung Cancer Foundation of America (LCFA), the National Lung Cancer Partnership

(NLCP), the American Cancer Society (ACS), and the American Lung Association (ALA) are among the most prominent groups (Genentech and Astellas Oncology, 2012). The LCFA provides research grants and supports use of molecular testing of people diagnosed with NSCLC; the organization uses its web site, publications, and events to encourage patients to be tested. The ACS and ALA focus on primary prevention, increasing early detection, and providing educational information for the lay public and epidemiologic statistics for researchers. The NLCP is the only organization with a formal ongoing campaign to increase EGFR testing of lung cancer patients; as mentioned above, the campaign is being conducted in collaboration with the Lung Cancer Mutation Consortium (National Lung Cancer Partnership, 2012).

Health care professional associations. There are a number of non-profit organizations representing health care professionals dedicated to improving cancer patient care and treatments; among the more prominent are the American Society of Clinical Oncology (ASCO); Community Oncology Alliance (COA); Oncology Nursing Society (ONS); and the American Association for Cancer Research (AACR).

With over 30,000 members, ASCO is the second largest organization representing cancer care specialists and researchers in the U.S. (American Society of Clinical Oncology, 2012); they are "committed to conquering cancer through research, education, prevention, and delivery of high quality patient care." ASCO is the preeminent physician organization in the oncology field (self-reported). In their recently published report, *Accelerating Progress Against Cancer: ASCO's Blueprint for Transforming Clinical and Translational Cancer Research*, ASCO shares its ten-year vision for making cancer research and care significantly more personalized, efficient, and effective (American Society of Clinical Oncology, 2012).

ASCO is one of two major organizations that promulgate clinical practice guidelines outlining appropriate methods of treatments and patient care. The other organization is the National Comprehensive Cancer Network (NCCN), which is a non-profit alliance of 21 major U.S.-based

cancer centers dedicated to improving the quality, effectiveness, and efficiency of oncology practice to improve the lives of cancer patients (American Society of Clinical Oncology, 2012). Both organizations promote the importance of continuous quality improvement in cancer care and the development and dissemination of clinical practice guidelines for use by health care professionals, other health care decision-makers, patients, and the public.

The COA is the only professional organization dedicated solely to supporting community oncology practice (Community Oncology Alliance, 2012); its primary focus is lobbying Congress to increase reimbursement rates for office-based oncology care and treatment.

The ONS is the largest organization of oncology professionals in the U.S. (and the world) with over 35,000 members from oncology nursing and other allied health professions (Oncology Nursing Society, 2012). ONS is dedicated to excellence in patient care, research, education, and nursing administration. Their focus is on finding and sharing practical ways of enhancing care of people with cancer rather than on drug treatment.

The AACR is the oldest and largest oncology research organization in the world (American Association for Cancer Research, 2012). With over 34,000 members throughout the world, including translational and clinical researchers, health care professionals, and cancer patients and advocates, AACR fosters and supports research in cancer and biomedical science and accelerates dissemination of new research findings in scientific and medical communities. The AACR funds a number of research fellowships and grants in lung cancer research; none focuses currently on the role of EGFR mutations in predicting treatment outcomes. There have been a number of studies presented on this subject at AACR meetings over the past eight years; however, there is currently no organized effort to encourage use of EGFR testing in routine clinical practice.

Managed care organizations. Managed care organizations (MCO) play a combination role of health insurer, health care delivery, and administration; their primary purpose is reducing unnecessary health care costs without compromising quality (Medline Plus, 2012). They provide comprehensive health services to plan enrollees for a contracted per member monthly fee.

MCOs use a number of different strategies for reducing health care costs including providing economic incentives to physicians and patients for choosing less costly treatment options; requiring prior authorization of a medication or service to justify the medical necessity before providing it to a patient; increasing beneficiary cost sharing for non-preferred medications; placing controls on hospital admissions and lengths of stay; providing incentives for selecting outpatient vs. inpatient services; assigning case managers for high risk patients and those with complex conditions; and aggressively contracting provider rates (American Medical Association Council on Medical Service, 2004).

In 2011, 210 million Americans—including over 11 million covered by Medicare and over 39 million covered by Medicaid--were covered by managed care plans (Centers for Medicare and Medicaid Services, 2012; MCOL; The Henry J. Kaiser Family Foundation). The largest purchasers of managed care services are employers and the Centers for Medicare and Medicaid Services. Fifty-five percent of Americans have employer-based health insurance and 90% of those individuals are enrolled in managed care plans (U.S. Census Bureau, 2012).

It is estimated the value of the targeted cancer drug market will increase to $51 billion in 2015 (Gochenhauer, 2012). With the cost of cancer medications growing at 20% or more per year, payers are increasing efforts to curtail costs without reducing quality of care (The American Journal of Managed Care, 2012; Snyder, 2012). A recent survey revealed managed care administrators believe almost one-quarter of current cancer care costs can be eliminated without compromising health outcomes; over eighty percent also believe inappropriate use of medications is a major driver of excess costs. Oncologists and MCO administrators anticipate a significant

increase in the aggressiveness of payer plans over the coming years in an attempt to reign in medication costs (The American Journal of Managed Care, 2012).

Requiring physicians to obtain prior authorization (PA) from the health plan before prescribing certain high cost medications is the most common lever used by managed care organizations to control costs of cancer care and reduce inappropriate prescribing (Farina K. , 2012; The American Journal of Managed Care, 2012). Prior authorization requirements are based most often on treatment recommendations found in recognized drug compendia, such as the American Society of Clinical Oncology and the National Comprehensive Cancer Network treatment guidelines. Although prior authorization requirements can decrease spending on oncology medications, their true impact on overall cost of medical care and clinical outcomes is unclear (Fischer, 2004; Hamel, 2004; Holcombe, 2011; MacKinnon, 2001).There is conflicting information about the percentage of MCOs requiring oncologists to perform biomarker testing as a condition for prior approval for coverage of oral oncology agents (Gochenhauer, 2012; The Zitter Group, 2012). In the 2011, respondents to the Kantar Health Oncology Market Access U.S. Oncologist Survey involving more than half of the community and hospital-based oncologists in the U.S. reported the three largest health plans in their area required biomarker testing as part of the prior approval requirements for coverage of erlotinib and gefitinib (Gochenhauer, 2012). However, a survey of 450 health plan directors conducted by the Zitter Group in the same year indicated very few of the plans surveyed required pretreatment EGFR testing as a condition of paying for erlotinib therapy, which is consistent with the Lynch data presented in part one of chapter two (Alt, 2011; Lynch J. A., 2013; The Zitter Group, 2012). Predictably, plans claimed their prior approval requirements for erlotinib are less about cost containment and more about limiting inappropriate prescribing. However, given the fact EGFR testing is the best method available currently for identifying patients likely to benefit from erlotinib and few payers require it as a condition of prior approval, it is reasonable to assume, despite the assertions of managed

care administrator, the primary driver behind prior approval requirements at the moment is cost control rather than quality.

Based on the same survey by the Zitter Group, lack of testing requirements for erlotinib prescribing may soon be outdated. Over 70% of plan directors expect to implement prior authorization guidelines requiring use of biomarker testing as a condition of coverage of certain targeted cancer medications in the coming years (Gochenhauer, 2012). Because health plans cover the vast majority of Americans, their failure to require and/or provide coverage for EGFR testing is a major barrier to use of molecular tests. However, MCOs can increase use of pretreatment EGFR testing by adding it to the prior authorization requirements for covering erlotinib (Aspinall, 2007).

Changing Clinical Practice

Intellectually, most cost-effective advances in health care make sense and one could logically assume they will be assimilated rapidly into routine clinical practice. However, this is usually not the case (Freemantle, 1995; Fuchs, 2011; Oxman, 1995). The traditional "trial and error" method of diagnosing and treating disease has been passed down from generation to generation of physicians leading many to reject more prescriptive approaches that impinge on a physician's clinical autonomy and judgment (Aspinall, 2007). Translation of research into clinical practice is anything but assured (Grimshaw J. M., 2012). It takes an average of 17 years for even the most important medical advances documented in the clinical literature to be integrated widely into clinical practice; in fact, in most cases adoption remains spotty for almost two decades after introduction of an innovation (Institute of Medicine, 2001).

Under-treatment and overtreatment of disease are common. Evidence suggests between 20 to 30% of patients in the U.S. receive care that is not needed or is potentially harmful leading to poor health outcomes, unnecessary expense, and higher mortality (Grimshaw J. M., 2012; Institute of Medicine, 2001; Rowland, 2004; Schuster, 2005). It is certainly true in the case of patients with

advanced or metastatic NSCLC; failure to test patients for genetic mutations before selecting from among available treatment options has serious consequences for patients and society in terms of morbidity, mortality, and cost.

Information Management

Information management is one of the primary barriers and contributors to slow adoption of medical technologies (Grimshaw J. M., 2012). The tremendous volume of clinical literature published each year makes keeping up with the latest findings a daunting task, especially for clinicians trying to balance busy practices and personal lives.

In addition to being targets of medical literature, physicians, like everyone else are being bombarded with non-scientific medical information and communications aimed at the public. As mentioned previously, news about cancer treatments is often exaggerated by lay media, which can lead consumers (health care professionals and patients) to believe study results are applicable to all patients. Unfortunately, the first publication of medical findings tends to show a more dramatic treatment effect than can be expected from use of a treatment in a broader patient population because strict study inclusion and exclusion criteria limit participation to a highly selected patient population that may have little in common with other patients with the same disease. Even when study results are published in major highly respected peer reviewed medical journals, they can be proven false or exaggerated over time as data from other studies accumulates, which points to a major drawback of changing clinical practice based on early published results.

Individual studies of interventions aimed at improving quality of medical care rarely provide sufficient evidence to motivate physicians to change their behavior (Dornbusch, 2006; Green, 2007). However, there are instances in the oncology world where early observational research has led to rapid, large-scale implementation of new treatments before clinical benefit was demonstrated in a less rigorously selected population of patients. One example is a decade-

long very public battle over use of autologous bone marrow transplant (ABMT) for the treatment of breast cancer resulting from publication of early clinical data showing promising results that drove early and rapid adoption of the treatment approach.

In 1988, an article in the *Annals of Internal Medicine* suggested that ABMT, which is a very involved, dangerous, and expensive procedure, was an effective treatment for advanced and metastatic breast cancer (Antman, 1988). The publication reviewed 27 separate studies involving 17 women; the reported response rate, defined as tumor shrinkage of greater than 50%, was 58%. There were no controls in any of the studies. In early 1989, the *Annals* published a review of results from another 159 women who had undergone ABMT (Cheson, 1989); there was an 80% response rate in these patients. Even though the authors of these two papers cautioned readers about the need to conduct randomized controlled trials, they concluded ABMT was superior to the best available therapies. There was no corroborating proof the procedure was effective but the media showed no restraint when reporting results; among the publications reporting results without caveats were the *Journal of the National Cancer Institute* (Mahaney, 1989) and the *Los Angeles Times* (Maugh, 1990).

In December 1989, the *Washington Post* reported the results of a 20 woman study conducted by Johns Hopkins University "a partial success" and went on to note ABMT cost $75,000 to $100,000, but insurers and Medicaid usually—but not always—covered the cost (Squires, 1989). That article, along with other positive media reports, articles in medical publications, breast cancer advocacy group lobbying, and the personal agendas of a small number of fraudulent oncologists led to a presumption of treatment effectiveness, which touched off a firestorm in the media, courts, Congress, and medical circles over the refusal of insurance companies to pay for "experimental" therapies (Welch, 2002).

The tide turned on ABMT a decade later at the widely attended 1999 annual meeting of ASCO, with the presentation of the outcomes of four randomized controlled trials disproving the value of ABMT as a breast cancer treatment. A subsequent editorial in the *New England of Journal Medicine* declared the treatment ineffective and unproven, and recommended it be abandoned in favor of more promising experimental treatments (Lippman, 2000). The results of these studies were reported widely in the popular press and used by insurance companies—once forced to pay for the unproven treatment—to deny claims. Unfortunately, poor clinical judgment and massive public pressure led to over 42,000 unnecessary and dangerous procedures at an average cost of $80,000 per person (Mello, 2001). The case outlined above serves as an ongoing reminder to oncologists (and other medical professionals) of the dangers associated with rapid adoption of unproven treatment modalities. One of the mechanisms used to reduce the risk of early adoption of questionable or unproven treatments is publication of clinical practice guidelines.

Clinical Practice Guidelines

Clinical practice guidelines (CPGs) are systematically developed statements applying to specific diseases, treatments, or clinical conditions or situations created by clinical experts after rigorous analysis of the best available clinical research evidence. CPGs guide appropriate patient care and help health care professionals and patients make better-informed treatment decisions (Browman, 2005; Cabana M. D., 1999; Field, 1990; Field, 1992; Wong R. K., 2012).

As mentioned earlier, two highly respected and influential professional organizations—ASCO and NCCN--promulgate lung cancer treatment guidelines, which include recommendations for pretreatment EGFR molecular testing of tumors of patients with advanced or metastatic NSCLC (American Society of Clinical Oncology, 2011; Browman, 2005; National Comprehensive Cancer Network, 2012). Both organizations include clinical experts on their guideline development teams, but vary in their conformity to other characteristics considered essential to development of

trustworthy guidelines (Browman, 2005), which could theoretically influence the rate of guideline adoption. The ASCO process is more explicit in how evidence is analyzed and interpreted to satisfy the due diligence requirements of an evidence-based approach; NCCN relies more heavily on the implicit knowledge and judgment of the clinical experts on the panel.

ASCO guidelines. In 2011, ASCO published a Provisional Clinical Opinion (PCO) on EGFR testing in NSCLC updating recommendations made previously in the ASCO Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer (American Society of Clinical Oncology, 2011). The PCO recommends testing all stage IV NSCLC patients for the presence of EGFR mutation before prescribing erlotinib (American Society of Clinical Oncology, 2011).

NCCN guidelines. In addition to issuing treatment guidelines recommending pretreatment EGFR testing of patients with advanced or metastatic NSCLC, NCCN established a task force to help educate the oncology community about the terminology associated with genetic tumor markers. They also provide information about the current state of biomarker validation in glioma, breast cancer, colon cancer, lung cancer, prostate cancer, and acute myelogenous leukemia (Febbo, 2011). The task force report: "Evaluating the clinical utility of tumor markers in oncology," is intended to help oncologists understand the science and technology behind using molecular testing when diagnosing and treating these six different types of cancer.

Clinical Practice Guideline Implementation

Theoretically, guidelines should improve quality of care by decreasing deviation from accepted standards of care (Cruz-Correa, 2001); however, improvements in quality depend on guidelines being applied consistently in medical practice and, in most cases, there is a distinct gap between published guidelines and actual clinical practice (Browman, 2005; Roila, 2004). Even though physicians bear responsibility for providing care that is consistent with local and national

standards, there are several barriers to implementing guidelines (The Italian Group for Antiemetic Research, 1998). They include awareness, individual knowledge and ability to correctly interpret available evidence, clinical experience, respect for clinical experts involved in guideline development, the willingness to change and time it takes practitioners to integrate guidelines into their individual practice styles, self-efficacy or belief the physician can successfully apply the guideline when caring for patients, and personal aversion to practicing "cookbook" medicine (Cabana M. D., 1998; Cabana M. D., 1999; Kaisser, 2005; Wong R. K., 2012).

It is important to recognize and understand the gap between published guidelines and current practice patterns, so the variation can be taken into account when planning guideline implementation. Unfortunately, while there are widely accepted processes for creating strong, evidence-based guidelines, there is no standard or proven approach guaranteeing successful guideline implementation.

The Cochrane Effective Practice and Organization of Care (EPOC) group has studied common strategies for motivating clinicians to adopt clinical practice guidelines. Interventions studied include printed education materials; medical education meetings; educational outreach visits; opinion leaders; audit and feedback; reminders; and financial incentives. The purpose of the research was to determine which of the dissemination and implementation approaches is most effective (Francke, 2008; Grimshaw J. M., 2004; Medves, 2010; Wong R. K., 2012).

Technology-Related Constraints

Later in this chapter, various interventions shown to be more or less effective in motivating physicians to change the way they practice medicine are reviewed. First, however, it is important to consider two intertwined technology-related barriers unique to genomic testing technologies; they likely play a role in physician and patient perception of and willingness to use molecular testing; they

include lack of genomics knowledge and education, and concerns about medical privacy and genetic discrimination.

Genomics knowledge and education. Recent genomic discoveries have increased dramatically the understanding of the genetic basis of disease, including cancers, by revealing complexities hidden in the human genome (Feero, 2011). The early stage of the genomics revolution from 1990 through today has yielded more clinically important advances than any period of discovery in western medicine (Feero, 2011; Lander, 2011). In 1990, the genetic basis was known for approximately 2% of over 7,000 inherited conditions resulting from changes in the DNA of a single gene; today, the molecular basis is known for over 40% of these conditions, which is a 20-fold increase in a little over twenty years. Other diseases, such as cancers, have more a complex molecular basis resulting from inheriting DNA from involvement of more than one gene, spontaneous mutations, environmental influences, or a combination of factors.

Applying advanced technologies and discoveries made in the study of more complex diseases, such as cancer, heart disease, and diabetes, have led to significant improvements in understanding of the genetic basis of these common conditions, which, in turn, has led to changes in the approach to characterizing and treating conditions once thought to be homogeneous diseases (Manolio, 2010). Over one thousand genetic variations have been shown to be associated with more complex conditions, with many being previously unknown or unsuspected biological causes (Aspinall, 2007; Feero, 2011). Unfortunately, these discoveries have not led to significant changes in the way most physicians diagnose and treat patients.

One major factor to contributing to the delay in adoption of genomic technologies is the need for physicians to have a better understanding of genomics and the implications for their clinical practice, along with the knowledge needed to communicate effectively with their patients (Feero,

2011). The Human Genome Project (HGP) was the first and most public effort to expand the understanding of the genetic basis of disease (Collins, 1997).

Dr. Francis Collins, former director of the National Human Genome Research Institute (NHGRI), is a leading proponent of finding and implementing practical applications of the knowledge gained from mapping the human genome. Even before the human genome map was completed and published in 2003, Dr. Collins identified education as one of the most important elements in transforming the knowledge gained from the HGP into clinical benefits for patients. Physicians need to understand the role of genomics, the implications of test results, how genomics can be used to improve quality of care and clinical outcomes, and be able to communicate clearly to patients the limitations, risks, and benefits associated with genetic testing.

Results from a recent landmark study of 800 U.S.-based practicing physicians indicate 80% of physicians believe personalized medicine will influence their medical practice; however, most admitted their current knowledge and understanding of genomics is lacking (CAHG, 2011). In fact, only 30% of oncologists surveyed said they are "very familiar with current issues and advances in personalized medicine." A majority of physicians surveyed have "low confidence in their ability to use and apply molecular diagnostics testing within their practice."

In addition to physicians' self-professed gaps in understanding of genomics, a survey of 1,000 Americans revealed the U.S. public is skeptical of physicians' knowledge and capability of using genetic information to understand and optimize their health (Cogent Research, 2011). Fewer than one in five (17%) Americans believe their physician is up-to-date and sufficiently knowledgeable about genomics-based medicine. A slightly higher percentage (21%) believes their physician is capable of explaining genomics-based medicine in a way that is understandable.

Genetic privacy and concerns about genetic discrimination. Another genomic-specific issue raising concerns for both physicians and patients is medical privacy and the potential impact of

genomic testing on employability and insurability. In May 2009, the Genetic Information Non-Discrimination Act (H.R. 493), also known as GINA, became law (National Human Genome Research Institute, 2012); it prevents employers and insurers from discriminating against individuals based on the results of genetic tests. However, these protections do not apply to Tricare military health plan participants, the Veteran's Administration, the Indian Health Service, or individuals covered by federal employee health benefit plans (GINAhelp.org, 2010).

Although policy and patient advocates believed passage of GINA would ease the fear of genetic discrimination, physicians and their patients remain concerned (Genetics Home Reference, U.S. National Library of Medicine , 2012). Over 90% of physicians who responded to a recent Cogent study expressed concerns about potential misuse of test results by insurance companies and 60% are worried about the possible impact on patient employment (Cogent Research, 2011). Patient anecdotes about experiencing discrimination based on genetic information abound, which further undermines the belief the benefits of testing outweigh the risks; according to the Equal Employment Opportunity Commission report for 2011, there were 245 genetic discrimination reports filed and monetary awards averaged $500,000 (Equal Employment Opportunity Commission).

Practically speaking, EGFR testing determines a patient's likelihood of responding to treatment and does not predict a person's likelihood of developing lung cancer. These tests do not yield information that can be used as a source of discrimination; however, people may not understand the distinction or believe this type of testing is different from diagnostic testing. By the time the molecular test is done, insurers already know the patient has lung cancer based on medical claims filed previously; the test provides no additional disease-related information that can be used to discriminate against the patient. It is conceivable however, based on current clinical practice guidelines, an employer or insurer could deny coverage for erlotinib if a patient does not have an EGFR mutation that makes them likely to benefit from the medication.

Influencing the Clinical Behaviors of Physicians: What Works and What Does Not?

Efforts aimed at changing physician behavior can range from simple and relatively low cost to very time-consuming, complex, and prohibitively expensive. This section outlines a number of strategies and tactics aimed at motivating physicians to change their clinical practice behaviors. Unfortunately, few have proven successful and, in most cases, the magnitude of change has been small. When possible, information relating to interventions used specifically to influence oncologists has been included.

As of August 2011, the EPOC had evaluated over 7,000 randomized and quasi-experimental studies in more than 80 systematic reviews of professional, organizational, financial, and regulatory interventions. They identified over 300 systematic reviews of behavior change strategies used to influence physicians, which they have synthesized into a small number of major categories including printed educational materials; educational meetings; educational outreach; local opinion leaders; audit and feedback; reminders, and financial incentives (Cochrane Effective Practice and Organisation of Care Group, 2012; Grimshaw J. M., 2012). Additionally, there are hundreds of published studies not included in EPOC reviews because they did not meet the stringent inclusion criteria.

Interventions can be one-size-fits-all, tailored, or multi-faceted. Unfortunately, very few studies compare specific interventions to other interventions, so it is often difficult to determine the presence of affect or the size of the effect on physician behaviors and clinical outcomes. One truth emerging from the literature is change is more easily driven and sustainable when the behavioral targets of change are simple rather than more involved or complex (Satterlee, 2008).

Printed education materials. Disseminating scientific information and clinical practice guidelines in print is a popular method of communicating scientific information to physicians. Printed materials have a self-life and can be read at a person's convenience, referred to in the

future, and passed along to colleagues (Giguère A. L.-K., 2012); in general, printed materials are intended to address specific knowledge or skill gaps of physicians (Grimshaw J. M., 2012). Printed materials, defined by EPOC as "distribution of published or printed recommendations for clinical care, including clinical practice guidelines", are intended to increase health care professionals' awareness, knowledge, attributes, and skills leading to improvements in patients' health and health outcomes.

The category of printed materials has expanded to include electronic dissemination of clinical information and educational materials, which is an increasingly popular method of communicating and acquiring medical knowledge. Print and electronic communications are popular channels due to their relatively low cost and ease of development. Although there are set-up charges involved in electronic communications, dissemination costs are extremely low making it much more cost effective than printing and distributing educational materials by sales representatives or direct mail. However, electronic communications pose added risks because it is easy for anyone to disseminate medical or clinical information, which, as noted above, can result in changes in clinical practice that harm patients.

The Cochrane Collaborative reviewed studies using printed and electronic educational materials to determine their impact on clinical practice and patient health outcomes, and to determine whether any specific characteristics (content, format, etc.) increase the effectiveness of printed materials in influencing health care professionals (Giguère A. L.-K., 2012). They reviewed 45 studies including 14 randomized clinical trials (RTCs) and 31 interrupted time series (ITS) analyses; all but one compared printed or electronically distributed materials to doing nothing.

The formal review suggests printed and electronic materials result in very slight improvements in clinical practice; but they are, in general, poor vehicles for disseminating clinically important and potentially practice changing information (Dornbusch, 2006; Jamtvedt,

2006; Oxman, 1995; Roila, 2004). Because of the lack of comparative trials, there is insufficient evidence to estimate the impact, if any on patient outcomes (Giguère A. L.-K., 2012; Oxman, 1995). There is, however, limited evidence that an article published in *The New England Journal of Medicine* can increase oncologists' awareness of new treatment-related data (Green, 2007).

Medical education meetings. Conferences, lectures, teaching, and training sessions involving two or more health care professionals comprise the category of educational meetings (Grimshaw J. M., 2012; Reeves, 2009). There are two types of meetings, those with an interactive component and didactic sessions; they used to improve collaboration and health outcomes. Research indicates interactive education is more effective than didactic lectures at changing physicians' knowledge and actions (Satterlee, 2008); in fact, didactic presentations, including traditional continuing medical education (CME) programs used commonly to impart new clinical information to practitioners, are generally ineffective. Pairing didactic lectures with interactive sessions is as effective as interactive sessions alone, but is more costly than one either alone. There have not been any placebo-controlled studies published assessing the impact of educational meetings.

Evidence suggests presentation of phase III data from clinical trials of cancer therapies at major medical meetings, such as ASCO, can results in swift and unexpected change in oncologists' prescribing behavior, as evidenced by the earlier example involving use of ABMT as an advanced breast cancer treatment. Unfortunately, as that situation suggests, early adoption of oncology treatments based on incomplete or unpublished clinical trials—even though presented at a prestigious medical meeting--does not always lead to improvements in patient outcomes (Green, 2007). Assumptions have been made that published or presented phase II clinical trial data would also influence physician behavior, but there is little evidence supporting this belief.

Educational outreach. Educational outreach visits, also known as academic detailing or educational detailing, involve a trained individual ("detailer"), subject matter expert, or local

opinion leader visiting a physician at their practice site to motivate the physician to change a specific practice-related behavior (O'Brien, 2008); occasionally, these visits involve feedback. Academic detailing has become popular during the past decade as a way for payers (government and private) to influence physicians to prescribe less costly treatments or use less costly interventions and technologies. Educational visits can lead to small to moderate improvements in patient care albeit at a high cost for recruiting, training, and paying educators, in addition to the lost productivity of the physicians engaged in these meetings (O'Brien, 2008; Roila, 2004). Combining visits with other methods of influencing behavior listed in this section is more effective than visits alone (Satterlee, 2008). Mason and colleagues found, despite high costs, academic detailing could be a cost effective method of changing physician behavior depending on the goal of the intervention (Mason, 2001).

Although, there are many examples of how this type of intervention has motivated prolonged change in prescribing behavior among physician in other specialties, only limited research exists regarding the effectiveness of academic detailing in changing oncologists' prescribing behaviors. One study evaluated the ability of detailers to increase oncologists' prescribing of anti-emetic medications used to prevent or treat nausea and vomiting in cancer patients undergoing chemotherapy in accordance with clinical practice guidelines. There was a positive impact in patients undergoing treatment with a medium to high degree of emetogenicity (ability to induce vomiting) (Roila, 2004). However, prescribing of anti-emetics for patients receiving chemotherapy with a lower potential of causing nausea and vomiting decreased in the study population while use was increasing among oncologists who had not received a visit.

Despite evidence academic detailing can be effective, no one knows for sure the specific attributes of trainers, physicians, topics, and number of visits associated with effective interventions (O'Brien, 2008). One thing is clear, it is unlikely educational outreach visits alone make a significant impact on clinical outcomes.

Opinion leaders. Opinion leaders, also known as thought leaders, are physicians or other health care professionals considered by their peers to be likeable, trustworthy, knowledgeable, and influential (Flodgren G. P., 2011; Grimshaw J. M., 2012). Opinion leadership depends on an individual's ability to influence informally the attitudes or behaviors of others. Respect is earned and maintained based on a person's perceived technical competency and accessibility. Likeability, while useful, is not an absolute requirement for effective thought leadership. Thought leadership is usually a lever for positive change; however, opinion leaders who oppose change can emerge as a significant barrier even when there is compelling clinical evidence supporting the need for and benefits of change (Majumdar, 2007).

The Cochrane Collaboration's 2011 systematic review of literature on opinion leader influence included 18 studies across a range of physician specialties and diseases; the effectiveness rate of the various interventions studied ranged from a 15% decrease in compliance with published guidelines to a 72% compliance with desired behaviors (Flodgren, 2011). Overall, the intervention groups had a 12% absolute improvement across studies in adherence to thought leader recommendations. Three of the studies used a multidisciplinary team approach to promoting evidence-based change. This approach showed even greater effect (18%), however, the design of these studies made it impossible to assess the impact of individual members of a team.

Evidence suggests opinion leaders can successfully influence the behavior of their peers; in fact, it appears to be one of the most effective methods of motivating physicians to change clinical behavior although the results of studies indicate effectiveness may vary depending on the individuals involved and the behavior(s) targeted for change. It comes as no surprise, therefore, that pharmaceutical companies, payers, health systems, and medical societies spend millions of dollars each year on thought leader identification, development, and training. However, focusing on

individual opinion leaders rather than multidisciplinary teams and/or multi-faceted interventions may limit the effectiveness of these efforts.

Audit and feedback. Audit and feedback involves comparing an individual health care professional's performance to standards of practice or clinical guidelines, and subsequently providing feedback on performance versus the standard (Ivers, 2012). It is one of the most widely studied and popular quality improvement interventions; it is similar to performance planning and reviews done by organizations to align employee work with organizational objectives. The goal of audit and feedback is motivating providers to adopt behaviors leading to increases in efficiency and/or improvements in quality of care and health outcomes.

The Cochrane Collaboration recently published a systematic review of 140 studies assessing the impact of audit and feedback on the clinical performance of health care professionals; more than 80% of the studies involved physicians practicing in outpatient settings. Slightly more than one-quarter of the studies assessed the impact of audit and feedback on prescribing behavior; a large majority of medication-related studies involved treatment of cardiovascular disease or diabetes. None of the studies involved cancer treatment. There was one published study involving oncologists, which was mentioned in the educational outreach section above (Roila, 2004). In addition to educational outreach, the investigators evaluated the effectiveness of audit and feedback. Neither approach had much impact on oncologists' prescribing behaviors. Effectiveness of this type of intervention hinges primarily on the attributes of the feedback element (Ivers, 2012; Jamtvedt, 2006; Roila, 2004). Feedback can be provided in written form, verbally, or both. It can be a one-time assessment or provided on an ongoing basis. Feedback can be provided by a supervisor or colleague, a peer, or recognized opinion leader from outside the organization or practice.

Audit and feedback can positively affect patient care (Grimshaw J. M., 2012; Ivers, 2012; Jamtvedt, 2006; Satterlee, 2008). However, the affect size varies widely from study to study ranging from negative to very large depending on the attributes of the feedback component;

generally, improvements are small to moderate. Attributes associated with positive results include poor pre-intervention performance; feedback given in writing and verbally by a supervisor or colleague multiple times over an extended period; and use of clear objectives and an action plan. Some evidence suggests audit and feedback may be more effective when used in combination with other methods, such as reminders; however, results of studies are mixed (Ivers, 2012; Jamtvedt, 2006).

Reminders. Reminders are used in health care settings for the same reason we use them in everyday life, except in this case they are tied to specific health care processes, medication prescribing, test ordering, or patient-physician encounters. Often physicians do not base clinical decisions on best evidence because of information overload or process breakdowns (McDonald, 1976). The primary purpose of reminders is closing the gap between clinical guidelines or standards of care and usual care. Reminders can effectively influence physician behaviors across a variety of clinical settings (Balas, 2000; Buntinx, 1993; Mandelblatt, 1995; Szilagyi, 2000; Wensing, 1994). They can be verbal, written, or electronic, and can be embedded in electronic health records or e-prescribing systems to serve as point-of-service prompts. Much of the research done in health care settings has involved computerized reminders because of the ease of implementation and data capture (Grimshaw J. M., 2012).

There are four types of written reminders, including generic cue sheets (e.g. sticky notes) with no response required; check lists requiring a recorded response; patient profiles with patient-specific information; and profile checklists also requiring a response be recorded (Pantoja, 2009).

Paper reminders effectively enhance outcomes to a small to moderate degree. Even though paper reminders are much less expensive and easier to implement than electronic reminders, they are easier to misplace, overlook or ignore.

A recent review of the effectiveness of electronic reminders in improving process and outcomes of care published by the Cochrane Collaboration evaluated the outcomes of 28 studies involving computerized reminders (Shojania, 2011). The review was an update of a previous publication by the same authors in 2009 (Shojania, 2009). Overall, computerized reminders have a small to moderate impact with the largest effect being process adherence at 4.2%, followed by vaccinations and test ordering (3.8%), and medication ordering (3.3%). A small number of studies included in the review produced statistically significant improvements; they all involved the computerized order entry system at Brigham and Women's Hospital. Otherwise, no specific reminder attribute or context was significantly associated with the magnitude of the observed behavior change attributed to computer-generated reminders (Loo, 2011; Shojania, 2011).

Financial incentives. Payers and physicians have different goals. Typically, payers seek to minimize health care costs while physicians are more interested in the health and quality of life of their patients (Holcombe, 2011). It is assumed physicians can be motivated by money to change clinical behaviors ranging from stricter adherence to clinical practice guidelines to making evidence-based treatment decisions to decreasing prescribing of expensive brand name medications. However, published results for this method are mixed (Farina K. , 2012; Feinberg, 2012; Flodgren G. E., 2011; Scott, 2011). The disparity in these study results is often attributed to the inherent conflict between extrinsic rewards and intrinsic physician motivators (Flodgren G. E., 2011); evidence suggests when intrinsic motivation is high, as it is in physicians, financial incentives may less effective in motivating behavior change.

There are five basic categories of incentives: (1) limited duration contracts; (2) payment for each service, episode, or visit; (3) payment for providing care for a specific patient population, such as low-income single mothers; (4) adhering to pre-specified treatment or quality targets; and (5) mixed systems. The second, third and fourth categories are generally effective in motivating change, although the affect is usually small; however, the same is not true of contracts or mixed systems.

Financial incentives are generally effective in improving processes of care, referrals, reducing hospital admissions, and lowering medication costs, and generally ineffective at improving adherence to clinical practice guidelines.

The use of financial incentives by payers is increasing despite lack of convincing evidence they improve quality of care or health outcomes (Flodgren G. E., 2011; Scott, 2011). There are a number of innovative performance-based payer programs, including some initiated by CMS, being implemented currently that are designed to improve quality of care, health outcomes, and adherence to clinical practice guidelines while reducing variations in care and costs. Data generated from these interventions will enhance the understanding of the impact of financial incentives on physician behavior and quality of care.

Summary

Part one of chapter two outlines options available for treating advanced NSCLC, and the risks associated with making empiric treatment decisions based on clinical, tumor, or patient-specific characteristics instead of using the genetic profile of the tumor as a guide. Opinion leaders in lung cancer treatment and guideline developers believe EGFR mutation testing helps oncologists make better informed and more precise treatment decisions. However, most oncologists have not yet integrated EGFR testing into clinical practice and very little is known about why, in the face of strong evidence and expert recommendations they have been slow to integrate EGFR testing into their care of patients with advanced or metastatic NSCLC.

Clearly, motivating physicians to change their clinical practice behaviors is no easy task. There are a myriad of factors influencing change--some positive and others negative. Several factors were reviewed in the beginning of part two of chapter two; they are listed in the table below.

Table 6 - Factors Influencing Physicians' Clinical Behavior	
Facilitators of change	**Barriers to change**
✓ Federal legislation and regulations ✓ Institute of Medicine ✓ Lung Cancer Mutation Consortium and the Biomarkers Consortium ✓ Patient advocacy organizations ✓ Health care professional associations ✓ Payers/MCOs ✓ Clinical practice guidelines	▪ Federal legislation and regulations ▪ Payers/MCOs ▪ Lack of motivation and time/clinical inertia ▪ Information and work overload ▪ Lack of knowledge or training in genetics ▪ Lack of buy-in for need to change ▪ Disagreement with proposed changes ▪ Perceived threat to personal autonomy ▪ Aversion to "cookbook" medicine ▪ Fear of genetic discrimination against patients by employers and insurers

There is no "magic bullet" for developing successful interventions aimed at motivating physicians to change their approach to diagnosing and treating specific diseases (Oxman, 1995). Developing formal clinical practice guidelines is an important first step in creating a path and rationale for change. However, motivating physicians to follow established guidelines remains a significant challenge.

The Cochrane Collaboration has published a number of formal systematic reviews of published studies exploring the effectiveness of specific physician behavior-change interventions. The interventions and their relative ability to motivate desired changes in physicians' clinical behaviors are shown in the table below.

Table 7 - Interventions and Their Impact on Physicians' Clinical Practice Behavior	
Intervention category	**Magnitude of effect**
Printed education materials (passive dissemination)	Small
Medical education meetings	
Didactic lectures	Small
Interactive sessions	Moderate
Didactic and interactive combined (no better than interactive alone)	Moderate
Educational outreach	Small to moderate
Opinion leaders	Large
Audit and feedback	Small to moderate
Reminders (paper and electronic)	Small to moderate
Financial incentives	
Limited duration contracts	No effect
Payment for each service, episode, or visit	Small
Payment for providing care for a specific patient population	Small
Adhering to pre-specified treatment or quality targets	Small
Mixed systems	No effect

Use of guideline implementation strategies remains an inexact science even after 40 years of study (Grimshaw J. M., 2004; Lomas, 1989; Osarogiagbon, 2011; Roila, 2004; Satterlee, 2008; Wong R. K., 2012). No single-pronged approach or combination of approaches works consistently and reliably to motivate changes in physician behaviors. However, complex multi-faceted interventions combining several of the approaches listed above show promise. Based on experience, it appears unlikely a universally successful single or multi-faceted approach will be identified anytime soon.

The benefits of increasing use of EGFR testing when selecting from among available treatment options for patients with advanced or metastatic NSCLC are unmistakable and appear to be irrefutable. Even so, adherence to EGFR testing recommendations remains much lower than might be expected after sustained efforts aimed at motivating oncologists to adopt testing as standard practice when caring for patients with lung cancer (Alt, 2011; Lynch J. A., 2013). As noted in the beginning of part two of chapter two, there are a number of factors at work facilitating use of EGFR testing; however, the criteria oncologists consider when deciding whether to use an EGFR test for a specific patient and the implications they have for increasing the use of EGFR testing by oncologists remain a mystery.

Chapter three in this manuscript outlines a research study designed to begin uncovering those factors and influencers. The insights and understanding gained from the literature review and key informant interviews with oncologists who treat patients with NSCLC will help inform the plan put forth in chapter five to motivate oncologists to increase their use of EGFR testing when treating patients with advanced or metastatic NSCLC.

APPENDIX B – INTERVIEW RECRUITMENT EMAIL

Email subject line: UNC research opportunity for oncologists treating lung cancer

Dear Dr. ((insert name)),

In collaboration with the Lung Cancer Initiative of North Carolina, we invite you to participate in an important study about the factors you consider when deciding whether to perform an EGFR test when treating a patient with advanced or metastatic lung cancer. My name is Patti Pozella and I am conducting a research study with oncologists who treat patients with lung cancer as a part of the requirements for a doctoral degree in Health Administration from the Gillings School of Global Public Health at UNC Chapel Hill. This is an independent study with no outside funding.

The study involves a brief telephone interview (between 20 to 30 minutes in length), scheduled at your convenience. We will be discussing factors you consider when deciding whether to order a genetic test to identify the presence of specific mutations in the epidermal growth factor receptor (EGFR) gene in patients being treated for advanced or metastatic non-small cell lung cancer. Although the understanding of the genetic basis of lung cancer has grown tremendously in recent years, little is known about what influences the decisions oncologists make about EGFR mutation testing, which is why your participation in this project is so important.

The interview will be recorded; however, use of a pseudonym during the interview will ensure your name is not associated with your responses. In addition, the information gathered during the 18 to 20 interviews being conducted will be aggregated and presented as group data. The file linking your name and contact information with your pseudonym will be encrypted and only I will know the password required to access the linking file. Deductive disclosure, which is the discerning of an individual respondent's identity and responses based on known characteristics of that individual, is possible, but unlikely due to the number of interviews being conducted for this research project. You may terminate the interview at any point in the discussion.

I understand you are very busy and I promise to be respectful of your time. If you are interested in participating, please respond affirmatively to this email and confirm that you treat patients with advanced or metastatic non-small cell lung cancer. Please also provide contact information (name, phone number and email address) for the person I should contact to schedule your interview.

Please feel free to email me at pozella@email.unc.edu if you have any questions about this research.

A committee that works to protect your rights and welfare reviews all research on human volunteers. If you have any questions or concerns regarding your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board for the University of North Carolina Chapel Hill at (919) 966-3113 or via email at IRB_subjects@unc.edu with study number # 13-2569 (7-26-2013).

APPENDIX C – INTERVIEW RECRUITMENT TELEPHONE SCRIPT

Hello Dr. ((insert name)),

In collaboration with the Lung Cancer Initiative of North Carolina, we invite you to participate in an important study about the factors you consider when deciding whether to perform an EGFR test when treating a patient with advanced or metastatic lung cancer. My name is Patti Pozella and I am conducting a research study with oncologists who treat patients with lung cancer as a part of the requirements for a doctoral degree in Health Administration from the Gillings School of Global Public Health at UNC Chapel Hill. This is an independent study with no outside funding.

I am hoping you will agree to participate in a brief telephone interview (between 20 to 30 minutes in length). We will schedule the interview at your convenience. We will be discussing factors you consider when deciding whether to order a genetic test to identify the presence of specific mutations in the epidermal growth factor receptor (EGFR) gene in patients being treated for advanced or metastatic non-small cell lung cancer. Although the understanding of the genetic basis of lung cancer has grown tremendously in recent years, little is known about what influences the decisions oncologists make about EGFR mutation testing, which is why your participation in this project is so important.

The interview will be recorded; however, I will be using pseudonyms during the interview process, which will ensure your name is not associated with your responses. I will also be aggregating the data across the 18 to 20 interviews I will be conducting and the data will be presented as group data. The file linking your name and contact information with your pseudonym will be encrypted and only I will know the password required to access the linking file.

It is possible, using deductive disclosure, which is the discerning of an individual respondent's identity and responses based on known characteristics of that individual, but unlikely someone will be able to identify your responses due to the number of interviews being conducted for

this research project. You may terminate the interview at any point in the discussion. I understand you are very busy and I promise to be respectful of your time.

1. Are you willing to participate?

   NO – terminate. Thank you for taking the time to talk with me today. Have a nice day.

2. Can you please confirm that you treat patients with advanced or metastatic non-small cell lung cancer?

   NO – terminate. Unfortunately, this research pertains to the treatment of lung cancer, so you are not eligible to participate, but I appreciate time you have spent talking with me today.

3. **C**an we schedule the interview now?

   NO. Who can I call to schedule a time for the interview (ask for name, email and phone number)?

   YES. Schedule and ask for MD's email address so a reminder can be sent.

Please feel free to call me at 919-607-4070 if you have questions or need to reschedule our interview.

A committee that works to protect your rights and welfare reviews all research on human volunteers. If you have any questions or concerns regarding your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board for the University of North Carolina Chapel Hill at (919) 966-3113 or via email at IRB_subjects@unc.edu with study number # 13-2569 (7-26-2013).

Thank you. I am looking forward to talking with you again soon.

APPENDIX D – INTERVIEW GUIDE

I. Introduction

Hello. I'd like to start by thanking you for talking with me today. My name is Patti Pozella and I'll be interviewing you. I am a doctoral student at the UNC Chapel Hill Gillings School of Global Public Health and the interview we're doing today is part of my dissertation, which is being done in partnership with the Lung Cancer Initiative of North Carolina. This is an independent research project with no outside funding.

We'll be discussing the factors you consider when deciding whether to use a genetic test to identify patients with non-small cell lung cancer who have specific mutations in the epidermal growth factor receptor gene (EGFR testing) prior to making treatment decisions. Your opinions, experiences, and observations are very valuable because little is known about what influences the decisions oncologists make about EGFR mutation testing.

Your participation is very important. I am interested in all of your ideas, comments, and suggestions. Please feel free to share your thoughts, talk candidly and elaborate during the discussion. We can revisit topics already discussed if you think of something you forgot to mention and would like to share.

I will be recording our discussion because I want to make sure I do not miss anything you have said. After the interviews are complete, I will carefully review and summarize the comments made by all of the oncologists participating in this research. The information used in the dissertation manuscript will be aggregated and presented as group data. You have my assurance that all of your comments will remain confidential and nothing you say will be connected with your name. To ensure your confidentiality, I will not refer to you by name, nor should you mention your own name during the audio recording of this interview. The file linking your name and contact information with your

assigned pseudonym has been encrypted and password protected. I am the only one who knows the password required to access the linking file.

Please confirm you are consenting to participate in this research study (wait for confirmation before proceeding).

II. Specialty and practice-related questions

1. I'd like to begin by asking whether you are a general or thoracic oncologist?
2. About how many people with advanced or metastatic non-small cell lung cancer do you treat in an average month?

2a. How many of those patients are newly diagnosed?

Probe, if necessary

It's OK to estimate the number of people you treat if you don't know for sure.

3. Can you please tell me little bit about where you work, such as whether it is a hospital or community-based practice; number of locations served; whether the practice is associated with a health system, local hospital, etc.?

Probe, if necessary

Do you practice in a:

a) Single location or multiple locations?
b) Rural or more urban setting [or both]?
c) Privately or publically owned facility?
d) Academic or non-academic setting?
e) Academic medical center, community hospital, community office-based practice or other type of setting?

EGFR testing questions

The next few questions focus on the factors you consider when deciding whether or not to order an EGFR test for a patient with advanced or metastatic non-small cell lung cancer.

4. Thinking about the patients that you treat with advanced or metastatic non-small cell adenocarcinoma of the lung, do you *NEVER, SOMETIMES OR ALWAYS* order EGFR testing before treating them?

IF ANSWER to Q. 4 is NEVER, SKIP to Q. 8

5. What percentage of your patients undergoes EGFR testing before starting treatment?

IF ANSWER to Q. 4 IS SOMETIMES OR ALWAYS:

6. What are your main reasons for ordering EGFR mutation tests for your patients?

   Probe, if necessary

   a) Institutional or practice protocol
   b) Insurer or managed care requirement
   c) Clinical practice guideline recommendation
   d) Clinical evidence or published literature
   e) Standard of care
   f) Personal experience with testing
   g) Peer suggestion or recommendation
   h) Patient request
   i) Is there anything else you would like to mention?

7. Is there any one thing that stands out in your mind as a particularly compelling reason to test your patients?

8. What is the main reason or reasons you decide not to order an EGFR mutation test for a patient?

Probe, if necessary

a) Test not available

b) Patient not fit for biopsy

c) Patient refuses

d) Time it takes to get results

e) Cost or patient can't afford it

f) Insurance (won't pay for the test, require prior authorization)

g) Clinical evidence or clinical practice guidelines

h) Peer suggestion/recommendation

9. Is there any one thing that is the most compelling reason for not testing your patients?

10. Do you expect your future use of EGFR testing to increase, decrease, or stay the same?

10a. Why?

IV. Closing

Before we wrap up the interview, I would like to ask a couple of quick questions that will help me to better characterize survey participants when analyzing the results.

11. How many years have you been in practice since completing your oncology training?

12. One last question…what percent of the patients you treat for lung cancer have advanced or metastatic non-small cell lung cancer? _____%

V. Thank you

Thank you for participating in my research project and for the time you spent with me.

REFERENCES

Agency for Healthcare Quality and Research. (2012, September 15). *Organizations & contacts*. Retrieved from AHRQ Agency for Healthcare Quality and Research Advancing Excellence in Health Care: http://www.ahrq.gov/about/organix.htm

Agency for Healthcare Research and Quality. (2012, August). *AHRQ at a glance*. Retrieved from AHRQ Agency for Healthcare Research and Quality: http://www.ahrq.gov/about/ataglance.htm

Agency for Healthcare Research and Quality. (2012, September 9). *Effective health Care Program What is comparative effectiveness research?* Retrieved from AHRQ Agency for Healthcare Research and Quality : http://effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1/

Alt, A. (2011, October 4). *EGFR assay vastly underused in lung cancer patients.* Retrieved from The Oncology Report.

Altecruse, S. K. (2010). *SEER stat fact sheets: lung and bronchus. Seer cancer statistics review, 1975-2007*. Retrieved from Statistics Epidemiology and End Results (SEER): http://seer.cancer.gov/statfacts/html/lungb.html

America Heritage Science Dictionary. (2005). (H. M. Company, Editor) Retrieved March 25, 2012, from http://www.thefreedictionary.com/exon

American Association for Cancer Research. (2012). *About us*. Retrieved from AACR: http://www.aacr.org/home/about-us.aspx

American Cancer Society. (2010, Sept 28). *Chemotherapy principles: An in-depth discussion*. Retrieved from American Cancer Society: http://www.cancer.org/Treatment/TreatmentsandSideEffects/TreatmentTypes/Chemotherapy/ChemotherapyPrinciplesAnIn-depthDiscussionoftheTechniquesanditsRoleinTreatment/chemotherapy-principles-goals-of-chemo

American Cancer Society. (2010). *Learn about cancer. Lung cancer (non-small cell).* Retrieved from American Cancer Society: http://www.cancer.org/Cancer/LungCancer-Non-SmallCell/DetailedGuide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer

American Cancer Society. (2013). *Cancer Facts & Figures 2013.* Retrieved from American Cancer Society: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf

American Cancer Society. (2013). *Lung cancer (non-small cell).* Retrieved January 21, 2012, from American Cancer Society: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf

American Hospital Association. (2012, January 3). *Fast Facts on US Hospitals.* Retrieved from American Hospital Association: http://www.aha.org/research/rc/stat-studies/101207fastfacts.pdf

American Medical Association Council on Medical Service. (2004). *Principles of Managed Care.* Retrieved September 25, 2012, from ama-assn.org: http://www.ama-assn.org/ama1/pub/upload/mm/363/principlesmanagecare.pdf

American Society of Clinical Oncology. (2011, December 1). *American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small cell lung cancer*. Retrieved from ASCO American Society of Clinical Oncology: http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Clinical+Practice+Guidelines/Lung+Cancer/American+Society+of+Clinical+Oncology+Clinical+Practice+Guideline+Update+on+Chemotherapy+for+Stage+IV+Non-Small+Cell+Lung+Cancer

American Society of Clinical Oncology. (2011, April 20). *American Society of Clinical Oncology Provisional Clinical Opinion: Epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small cell lung cancer considering first-line EGFR tyrosine-kinase inhibitor (TKI) therapy.* Retrieved from American Society of Clinical Oncology: http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Clinical+Practice+Guidelines/American+Society+of+Clinical+Oncology+Provisional+Clinical+Opinion%3A+Epidermal+Growth+Factor+Receptor+%28EGFR%29+Mutation+Testing+for+Patients+with+Advanced+Non-Sm

American Society of Clinical Oncology. (2012). *ASCO Profile*. Retrieved from American Society of Clinical Oncology: http://www.asco.org/ASCOv2/About+ASCO/ASCO+Information/ASCO+Profile

American Society of Clinical Oncology. (2012). *Research Blueprint.* Retrieved from American Society of Clinical Oncologists: http://www.asco.org/ASCOv2/Research+Resources/Research+Blueprint

Amler, L. C. (2005). Predicting clinical benefit in non-small-cell lung cancer patients treated with epidermal growth factor tyrosine kinase inhibitors. *Cold Spring Harbor Symposia on Quantitative Biology*, (pp. 483-488). Cold Spring Harbor.

Angulo, B. C.-G.-V.-A.-R. (2012, August 12). *A comparison of EGFR mutation testing methods in lung carcinoma: Direct sequencing, real-time PCR and immunohistochemistry.* Retrieved from PLOS One: http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0043842&representation=PD

Antman, K. a. (1988). Advanced breast cancer: High-dose chemotherapy and bone marrow autotransplants. *Annals of Internal Medicine, 108*, 570-574.

Ardizzoni, A. G. (1999, Sept). Induction chemotherapy followed by concurrent standard radiotherapy and daily low-dose cisplatin in locally advanced non-small-cell lung cancer. *British Journal of Cancer, 81*(2), 310-315. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2362873/?tool=pubmed

Arp, D. (2005, March/April). *The future of genomics: hope or hype?* Retrieved from America's Health Insurance Plans: http://www.ahip.org/content/default.aspx?docid=10765&pf=true

ASCO. (2012, June 1-5). *ASCO daily news.* Retrieved from ASCO annual meeting '12: http://chicago2012.asco.org/ASCODailyNews/lungcost.aspx

Aspinall, M. G. (2007, October). Realizing the promise of personalized medicine. *Harvard Business Review*(Reprint #R0710F), 1-10.

Association for Value-Based Cancer Care. (2012, January). *NCCN Expert Panel considers value, utilization of molecular testing in clinical practice.* Retrieved from Value-based cancer care: http://www.valuebasedcancer.com/article/nccn-expert-panel-considers-value-utilization-molecular-testing-clinical-practice

AstraZeneca. (2003, May 5). *Astra Zeneca receives FDA approval for new cancer drug Iressa (gefitinib, ZD1839).* Retrieved from Astra Zeneca Global: http://www.astrazeneca.com/Media/Press-releases/Article/20030505--ASTRAZENECA-RECEIVES-FDA-APPROVAL-FOR-NEW-CANCER-DRUG

AstraZeneca. (n.d.). *Methodologies for EGFR Mutation Detection.* Retrieved from EGFR M+: http://www.egfr-mutation.com/_mshost8902790/content/documents/EGFR-Test-Guide

Balas, E. A. (2000). Improving preventive care by prompting physicians. *Archives of Internal Medicine, 160*(3), 301-308.

Balko, J. M. (2006). Gene expression patterns that predict sensitivity to epidermal growth factor receptor tyrosine kinase inhibitors in lung cancer cell lines and human lung tumors. *BMC Genomics*, 289-303.

Beasley, D. (2012, June 15). *Drug Costs Becoming Bigger Issue In Cancer Care* . Retrieved from The Huffington Post: http://www.huffingtonpost.com/2012/06/15/drug-costs-cancer-care_n_1599307.html

Beil, L. (2009, June 9). *Targeted therapies: hope or hype?* Retrieved from Cure: http://www.curetoday.com/index.cfm/fuseaction/article.show/id/2/article_id/1133

Biomarkers Consortium. (2012, August 23). *The Biomarkers Consortium: What we do*. Retrieved from http://www.biomarkersconsortium.org/whatwedo.php

Blue of California. (2012, January). *Medicare Part D coverage criteria.* Retrieved from Blue of California: https://www.blueshieldca.com/sites/medicare/documents/PA_CY2012_TARCEVA_Erlotinib_MCweb.pdf

Bonomi, P. D. (2007). Selecting patients for treatment with epidermal growth factor tyrosine kinase inhibitors. *Clinical Cancer Research, 13*(15 supplement), S4606-S4612.

Breathnach, O. S. (2001, March 15). Twenty-two years of phase III trials for patients with advanced non-small-cell lung cancer: sobering results. *Journal of Clinical Oncology, 19*(6), 1734-42.

Brooks, M. (2012, April 20). *EGFR Mutation Guides Erlotinib in Advanced Lung Cancer.* Retrieved from Medscape: http://www.medscape.com/viewarticle/762406?src=nl_topic

Browman, G. P. (2005). Practitioners as experts: the influence of practicing oncologists "in the field" on evidence-based guideline development. *Journal of Clinical Oncology, 23*(1), 113-119.

Buntinx, F. W. (1993). Influencing diagnostic and preventive performance in ambulatory care by feedback and reminders. A review. *Family Practice, 10*(2), 219-228.

Cabana, M. D. (1998). Barriers to guideline adherence. *The American Journal of Managed Care, 154*(7), 1013-1017.

Cabana, M. D. (1999). Why don't physicians follow clinical practice guidelines? *Journal of the American Medical Association, 282*(15), 1458-1465.

CAHG. (2011, July 28). CAHG study highlights personalized medicine gap. Chicago, IL, USA. Retrieved from http://www.prnewswire.com/news-releases/cahg-study-highlights-personalized-medicine-gap-126321548.html

Calfee, J. E. (2006, Sep/Oct). The emerging market dynamics of targeted therapeutics. *Health Affairs, 25*(5), 1302-1308.

Cancer Research UK. (2012, January 10). *Cancer growth blockers (tyrosine kinase, proteasome, mTOR and PI3K inhibitors).* Retrieved February 20, 2012, from Cancer Help UK: http://cancerhelp.cancerresearchuk.org/about-cancer/treatment/biological/types/cancer-growth-blockers

Cassidy, A. A. (2010, May 20). *Health policy brief: Health reform's changes in Medicare.* Retrieved from Health Affairs: http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=17

Cataldo, V. D. S. C. (2011, March 10). Treatment of Non–Small-Cell Lung Cancer with Erlotinib or Gefitinib. *The New England Journal of Medicine, 364*(10), 947-955.

CDC Office of Public Health Genomics. (2012, August 23). *Genetic testing genomic tests by levels of evidence.* Retrieved from Center for Disease Control and Prevention: http://www.cdc.gov/genomics/gtesting/tier.htm

Centers for Medicare and Medicaid Services. (2012, April 5). *Accountable Care Organizations (ACOs)*. Retrieved from CMS.gov: http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ACO/index.html?redirect=/ACO/

Centers for Medicare and Medicaid Services. (2012, September). *Clinical laboratory fee schedule CY 2013 updates.* Retrieved from CMS.gov: http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Downloads/CY2013-Public-Meeting-New-Test-Codes-aeth.pdf

Centers for Medicare and Medicaid Services. (2012, May 25). *Medicaid managed care enrollees as of July 1, 2010*. Retrieved September 25, 2012, from cms.gov: https://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Downloads/2010July1.pdf

Centers for Medicare and Medicaid Services. (2012, April 25). *Medicare plan finder*. Retrieved from Medicare.gov The official US government site for Medicare: https://www.medicare.gov/find-a-plan/questions/home.aspx

Centers for Medicare and Medicaid Services. (2012, April 4). *Quality Initiatives - General Information*. Retrieved from CMS.gov: http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityInitiativesGenInfo/index.html

Centers for Medicare and Medicaid Services Center for Medicare and Medicaid Innovation. (2012, September 24). *Accountable Care Organizations (ACOs)*. Retrieved from CMS Centers for Medicare and Medicaid Services Center for Medicare and Medicaid Innovation: http://innovations.cms.gov/initiatives/ACO/index.html

Chernew, M. B. (2010, April 16). *Centers for Medicare and Medicaid Services.* Retrieved from CMS.gov: http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/Downloads/SpilloverEffects.pdf

Cheson, B. L.J. (1989). Autologous bone marrow transplantation: Current status and future directions. *Annals of Internal Medicine, 110*, 51-65.

Chustecka, Z. (2013, May 9). *Reflex testing of lung cancer tissue needs to be improved.* Retrieved from Medscape Medical News Oncology: http://www.medscape.com/viewarticle/803891

Chustecka, Z. (2013, April 5). *Test all adenocarcinomas, new lung cancer guidelines say.* Retrieved from Medscape Medical News Oncology: http://www.medscape.com/viewarticle/781998

Ciardiello, F. (2008). EGFR antagonists in cancer treatment. *The New England Journal of Medicine, 358*(11), 1160-1174.

CMS Centers for Medicare and Medicaid Services Center for Medicare and Medicaid Innovation. (2012, September 24). *Better health care, better health, and reduced costs through improvement*. Retrieved from CMS Centers for Medicare and Medicaid Services Center for Medicare and Medicaid Innovation: http://innovations.cms.gov/

Cochrane Effective Practice and Organisation of Care Group. (2012, October 16). *Welcome to the EPOC Ottawa website*. Retrieved from OHRI IRHO A Review Group of the Cochrane Collaborative : http://epoc.cochrane.org/

Cogent Research. (2011, January 25). Americans skeptical of physicians' knowledge of genomics. Cambridge, MA, USA. Retrieved from http://www.cogentresearch.com/news/Press%20Releases/CGAT_2010_Press%20Release_1_25_11.pdf

Collins, F. S. (1997). Preparing health professionals for the genetic revolution. *Journal of the American Medical Association, 278*(15), 1285-1286.

Community Oncology Alliance. (2011). *Community Oncology Alliance Position Statement on Health Care Reform*. Retrieved August 27, 2011, from Community Oncology Alliance: http://www.communityoncology.org/PositionStatement.aspx

Community Oncology Alliance. (2012). *Questions about COA*. Retrieved from Community Oncology Alliance: http://www.communityoncology.org/site/questions-about-coa.htm

Conaway, B. (2010, June). *Lung Cancer Health Center, Non-small cell lung cancer: advances in chemotherapy.* Retrieved from WebMD: http://www.webmd.com/lung-cancer/features/non-small-cell-lung-cancer-advances-in-chemotherapy

Cruz-Correa, M. G. (2001). The impact of practice guidelines in the management of Barrett esophagus. *Archives of Internal Medicine*, 2588-2595.

Dancey, J. (2007). Epidermal growth factor receptor inhibitors in non-small cell lung cancer. *Drugs, 67*(8), 1125-1138.

De Marinis, F. &. (2008). Clinical evidence for second- and third-line treatment options in advanced non-small cell lung cancer. *The Oncologist, 13*(Supplement 1), 14-20. Retrieved from www.TheOncologist.com

Di Maio, M. L.-M. (2010). Clinical assessment of patients with advanced non-small-cell lung cancer eligible for second-line chemotherapy: a prognostic score from individual data of nine randomised trials. *European Journal of Cancer, 46*(4), 735-743.

Dornbusch, D. A. (2006). How do US medical oncologists learn and apply new clinical trials information from press releases in nonmedical media? *The Oncologist*(11), 31-38.

Dowell, J. E. (2005). Chasing mutations in the epidermal growth factor in lung cancer. *The New England Journal of Medicine, 352*(2), 830-832.

Drugstore.com. (n.d.). Tarceva 150mg Tablets. Retrieved March 24, 2012, from http://www.drugstore.com/tarceva/150mg-tablets/qxn50242006401

Dunne, M. &. (2008, August 28). *EGFR inhibitors: Toxicities and strategies for effective management.* Retrieved September 28, 2008, from Medscape: http://cme.medscape.com/viewprogram/17187

Eberhard, D. A. (2008). Biomarkers of response to epidermal growth factor receptor inhibitors in Non–Small-Cell Lung Cancer Working Group: Standardization for use in the clinical trial setting. *Journal of Clinical Oncology, 26*(6), 983-993.

Edwards, P. J. (2009, July 8). *Methods to increase response to postal and electronic questionnaires (review).* Retrieved from Cochrane Library: http://onlinelibrary.wiley.com.libproxy.lib.unc.edu/doi/10.1002/14651858.MR000008.pub4/pdf/standard

Equal Employment Opportunity Commission. (n.d.). *Genetic Information Non-Discrimination Act Charges FY 2010-2011*. Retrieved September 25, 2012, from Equal Employment Opportunity Commission: http://www.eeoc.gov/eeoc/statistics/enforcement/genetic.cfm

Erikson, A. K. (2008). Powers of prediction predictive markers help oncologists match patients with the most effective treatments. *Cure, 6*(5), pp. 20-24.

Farina, K. (2012, September). How payers and oncologists really feel about oncology pathways. *The American Journal of Managed Care, 18*(Special Issue 4), SP188. Retrieved from http://www.ajmc.com/_media/_pdf/EBOsep.pdf

Farina, K. L. (2012). The economics of cancer care in the United States. *The American Journal of Managed Care, 18*(Special Issue 1), PS22-23. Retrieved from http://www.ajmc.com/publications/evidence-based-oncology/2012/2012-2-vol18-n1/The-Economics-of-Cancer-Care-in-the-United-States-How-Much-Do-We-Spend-and-How-Can-We-Spend-It-Better

FDA. (2009, June 19). Tarceva (erotinib) tablets September 2008. Retrieved from /www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm123017.htm

FDA. (2013, May 14). *FDA approves first companion diagnostic to detect gene mutation associated with a type of lung cancer*. Retrieved from US Food and Drug Administration : http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm352230.htm

Febbo, P. G. (2011). NCCN Task Force Report: Evaluating the clinical utility of tumor markers in oncology. *Journal of the National Comprehensive Cancer Network, 9*(Supplement 5), S.1-S.32. Retrieved November 15, 2012, from http://www.jnccn.org/content/9/Suppl_5/S-1.full

Feero, W. G. (2011). Genomics education for health care professionals in the 21st century. *Journal of the American Medical Association, 306*(9), 989-990. doi:10.1001/jama.2011.1245

Feinberg, B. A. (2012, September). Implementation of cancer clinical care pathways. *The American Journal of Managed Care, 18*(Special Issue 4), SP159-165. Retrieved from http://www.ajmc.com/_media/_pdf/EBOsep.pdf

Field, M. J. (1990). *Clinical practice guidelines: Directions for a new program.* Institute of Medicine. Washington, DC: National Academy Press. Retrieved from http://www.nap.edu/catalog.php?record_id=1626#toc

Field, M. J. (1992). *Guidelines for clinical practice: from development to use.* Washington, DC: National Academy Press.

Fischer, M. A. (2004, November 18). Medicaid prior-authorization programs and the use of cyclooxygenase-2 inhibitors. *The New England Journal of Medicine, 351*, 2187-2194. Retrieved from http://www.nejm.org.libproxy.lib.unc.edu/doi/full/10.1056/NEJMsa042770

Flodgren, G. E. (2011). *An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes (Review).* The Cochrane Collaboration. London: John Wiley & Sons, Ltd. Retrieved from http://onlinelibrary.wiley.com.libproxy.lib.unc.edu/doi/10.1002/14651858.CD009255/pdf

Flodgren, G. P. (2011, May 10). Local opinion leaders: effects on professional practice and health outcomes (Review). *Cochrane Database of Systematic Reviews*(8). doi:10.1002/14651858.CD000125.pub4.

Francke, A. L. (2008). Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Medical Informaiton Decision Making, 8*(38).

Freemantle, N. G. (1995). Implementing findings of medical research: The Cochrane Collaborative on effective professional practice. *Quality in Health Care*(4), 45-47.

Fuchs, V. R. (2011, May 26). The $640 billion question — why does cost-effective care diffuse so slowly? *The New England Journal of Medicine, 364*(21), 1985-1987.

Gandara, D. R. (2010, June 20). *Expert Analysis Lung Cancer CCO Independent Conference Coverage of the 2010 American Society of Clinical Oncology Annual Meeting.* Retrieved from Clinical Options: http://www.clinicaloptions.com/Oncology/Conference%20Coverage/Clin%20Onc%20June%202010/Tracks/Lung%20Cancer/Lung_Cancer/Pages/Page%201.aspx

Gawande, A. (2010, August 2). *Annals of Medicine Letting go. What should medicine do it if can't save your life?* Retrieved August 10, 2010, from The New Yorker Magazine: http://www.newyorker.com/reporting/2010/08/02/100802fa_fact_gawande?currentPage=all

Gazdar, A. (2010). Epidermal growth factor receptor inhibition in lung cancer: the evolving role of individualized therapy. *Cancer Metastasis Review, 29*, 37-48.

Gazdar, A. F. (2009, Aug 28). Review Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene, 28*(Supplement 1), S24–S31.

Genentech. (2010, April 16). FDA Approves Tarceva as a Maintenance Therapy for Advanced Non-Small Cell Lung Cancer. Retrieved from http://www.gene.com/gene/news/press-releases/display.do?id=12727&method=detail

Genentech. (2010, October). Herceptin (trastuzumab) final labelling text. Retrieved from http://www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf

Genentech and (osi) oncology. (2011, August). Highlights of prescribing information. *Tarceva (erlotinib) tablets*. NY.

Genentech and (osi) oncology. (2011, August). *Tarceva erlotinib tablets full prescribing information.* Retrieved from Genentech.

Genentech and Astellas Oncology. (2012, September 23). *tarceva for Advanced Non-Small Cell Lung Cancer Support Links*. Retrieved from Tarceva (erlotininb) Tablets: http://www.tarceva.com/professional/patient/links.jsp

Genentech Inc. (2012, April 22). *Tarceva Fact Sheet.* Retrieved from Genentech, A Member of the Roche Group: http://www.gene.com/gene/products/information/oncology/tarceva/factsheet.html

Genentech, (osi). (2010, May). Tarceva rash management guide. Retrieved from http://www.tarceva.com/docs/Tarceva_HCP_RashManagementGuide.pdf

Genentech, Astellas. (n.d.). Tarceva (erlotinib) in advanced non-small cell lung cancer and advanced pancreatic cancer. Retrieved March 24, 2012, from http://www.gene.com/gene/news/kits/biooncology/pdf/Tarceva_Product.pdf

Genetics Home Reference, US National Library of Medicine . (2012, September 24). *What is genetic discrimination?* Retrieved from Genetics Home Reference your guide to understanding genetic conditions: http://ghr.nlm.nih.gov/handbook/testing/discrimination

Giaccone, G. (2005). Epidermal growth receptor inhibitors in the treatment of non-small-cell lung cancers. *Journal of Clinical Oncology*, 3235-3242.

Giaccone, G. (2007). The potential of antiangiogenic therapy in non-small cell lung cancer. *Clinical Cancer Research, 13*(7), 1961-1970.

Giaccone, G. (2005). EGFR inhibitors: what have we learned from the treatment of lung cancer? *Nature Clinical Practice Oncology, 2*(11), 554-561.

Giguère, A. L. (2012). *Printed educational materials: effects on professional practice and healthcare outcomes (Review).* The Cochrane Library. John Wiley & Sons, Ltd. Retrieved from http://www.thecochranelibrary.com

GINAhelp.org. (2010, May). *Understanding GINA Genetic Information Non-Disrimination ACT.* Retrieved from GINAhelp.rg: http://www.dnapolicy.org/resources/GINAHelp052710.pdf

Global Conference Partners. (n.d.). *Our conference call services*. Retrieved from Free conference: https://www.freeconference.com/Services.aspx

Gochenhauer, G. (2012, January 31). *Personalized medicine: Biomarkers and the advent of new technologies to determine appropriate care in cancer.* Retrieved from Kanter Health: http://www.kantarhealth.com/docs/presentations/personalized-medicine-biomarkers-and-the-advent-of-new-technologies-to-determine-appropriate-care.pdf?sfvrsn=4

Green, M. R. (2007). Irinotecan-cisplatin therapy for patients with extensive-stage small cell lung cancer: use patterns among American medical oncologists 2000-2006. *Journal of Thoracic Oncology, 2*(10), 953-956.

Greenapple, R. (2012). *Accountable care organizations: implications for oncology.* Retrieved from Value-Based Cancer Care: http://www.valuebasedcancer.com/article/accountable-care-organizations-implications-oncologists

Gridelli, C. B. (2008, Jul). An international, multicenter, randomized phase III study of first-line erlotinib followed by second-Line cisplatin/gemcitabine versus first-line cisplatin/gemcitabine followed by second-line erlotinib in advanced non–small-cell lung cancer: treatment... *Clinical Lung Cancer, 9*(4), 235-238.

Gridelli, C. M. (2009, February 3). *Potential treatment options after first-line chemotherapy for advanced NSCLC: Maintenance treatment or early second-line?* Retrieved October 7, 2010, from The Oncologist: www.TheOncologist.com

Grimshaw, J. M. (2004). Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technology Assessment, 8*(6), iii-iv.

Grimshaw, J. M. (2012, May 31). Knowledge translation of research findings. *Implementation Science*, p. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3462671/.

Grossi, F. A. (2009, May). Impact of Third-Generation Drugs on the Activity of First-Line Chemotherapy in Advanced Non-Small Cell Lung Cancer: A Meta-Analytical Approach. *The Oncologist*, 497-510. Retrieved from http://theoncologist.alphamedpress.org/content/14/5/497.long

Hamel, M. B. (2004, November 18). Prior-authorization programs for controlling drug spending. *The New England Journal of Medicine, 351*(21), 2156-2157. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMp048294

Han, S. K. (2006). Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, k-ras mutation, and Akt phosphorylation. *Clinical Cancer Research, 12*(8), 2538-2544.

Herbst, R. S. (2007). Molecular signatures of lung cancer--toward personalized medicine. . *The New England Journal of Medicine, 356*(1), 76-78.

Hirsch, F. R. (2006, Nov 1). Molecular predictors of outcome with gefitinibin a phase III placebo-controlled study in advanced non-small-cell lung cancer. *Journal of Clinical Oncology, 24*(31), 5034-5042.

Holcombe, D. (2011, May). Oncology management programs for payers and physicians: evaluating current models and diagnosing successful strategies for payers and physicians. *Journal of Oncology Practice, 7*(3S), e46s–e49s. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3092461/

Huff, C. (2010, Spring). Long overdue genetic targets offer the latest hope in moving beyond chemo in the treatment of lung cancer. . *Cure*, 52-58.

Hurst, S. A. (2005). How physicians face ethical difficulties: a qualitative. *Journal of Medical Ethics, 31*, 7-14.

Institute of Medicine. (2001). *Crossing the quality chasm: A new health system for the 21st century.* Washington, DC. Retrieved from www.nap.edu/html/quality_chasm/reportbrief.pdf

Institute of Medicine. (2012, January 18). *About the IOM*. Retrieved from Institute of Medicine of the National Academies: http://www.iom.edu/About-IOM.aspx

Institute of Medicine. (2012, August 13). *National Cancer Policy Forum.* Retrieved from Institute of Medicine of the National Academies: http://www.iom.edu/Activities/Disease/NCPF.aspx

Ivers, N., J. G.-J. (2012). *Audit and feedback: Effects on professional practice and healthcare outcomes (review).* The Cochrane Collaboration. London: John Wiley and Sons, Ltd. Retrieved from http://onlinelibrary.wiley.com.libproxy.lib.unc.edu/doi/10.1002/14651858.CD000259.pub3/abstract

Jackman, D. M. (2009, April 15). Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clinical Cancer Research, 15*(16), 5267-5272.

Jamtvedt, G. Y. (2006). Does telling people what they have been doing change what they do? A systematic review of the effects of audit and feedback. *Quality and Safety in Health Care*(15), 433-436.

Janne, B. A. (2006). Effect of epidermal growth factor receptor kinase domain mutations on the outcome of patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors. *Clinical Cancer Research, 12*(Suppl 14), S4416-S4420.

Jemal, A. S. (2010). Cancer statistics 2010. *CA: A Cancer Journal for Clinicians*, 277-300.

John, T. L. (2009). REVIEW Overview of molecular testing in non-small-cell lung cancer: mutational analysis, gene copy number, protein expression and other biomarkers of EGFR for the prediction of response to tyrosine kinase inhibitors. *Oncogene*(28), S14–S23.

Johnston, J. B. (2006). Targeting the EGFR pathway for cancer therapy. *Current Medicinal Chemistry, 13*(29), pp. 3483-3492.

Kaiser Family Foundation. (2012). *Health care costs: A primer. Key information on health care costs and their impact.* Kaiser Family Foundation. Retrieved from http://www.kff.org/insurance/upload/7670-03.pdf

Kaisser, R. (2005). Antiemetic guidelines: are they being used? *The Lancet*(6), 622-625.

Kamel-Reid, S. G. (2012, April). EGFR tyrosine kinase mutation testing in the treatment of non-small-cell lung cancer. *Current Oncology, 19*(2), e67-74.

Keedy, V. L. (2011, May 20). American Society of Clinical Oncology Provisional Clinical Opinion: Epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non–small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. *Journal of Clinical Oncology, 29*(15), 2121-2127.

Keedy, V. L. (2011, April 11). Mutation testing for patients With advanced non–small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. *Journal of Clinical Oncology*, 2121-2127. Retrieved August 27, 2011

Kufe, D. W. (2003). *Holland-Frei Cancer Medicine. 6th edition.* Hamilton, Ontario, Canada: B. C. Decker. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK13873/

Lander, E. S. (2011). Initial impact of the sequencing of the human genome. *Nature, 470*(7333), 187-197.

Langreth, R. (2010, Dec 20). *Real Cancer Drug Breakthrough Is Astronomical Prices.* Retrieved from Forbes.com: http://www.forbes.com/sites/robertlangreth/2010/12/20/real-cancer-drug-breakthrough-is-astronomical-prices/

Lennes, I. (2011, June 29). M.D. Massachusetts General Hospital Cancer Center. *Treatment for metastatic disease and maintenance therapy. NCCN 2011 Congress series: respiratory tract cancers*. Durham, NC, USA.

Levenson, D. (. (2008, February). Targeted therapeutics in non-small cell lung cancer how molecular assays guide their use . *Clinical Laboratory News, 34*(2). Retrieved April 10, 2008, from http://www.aacc.org

Lippman, M. E. (2000). High-dose chemotherapy plus autologous bone marrow transplantation for metastatic breast cancer. *New England Journal of Medicine, 342*, 1119-1120.

Lomas, J. A.-P. (1989). Do practice guidelines guide practice? The effect of a consensus statemtn on the practice of physicians. *The New England Journal of Medicine, 321*(19), 1306-1311.

Loo, T. S. (2011). Electronic medical record reminders and panel management to improve primary care of elderly patients. *Archives of Internal Medicine, 171*(17), 1552-1557. Retrieved from http://archinte.jamanetwork.com/article.aspx?articleid=1105941

Lung Cancer Foundation of America. (2010, May 17). *Get your tumor tested...FREE!* Retrieved from Lung Cancer Foundation of America: http://www.lcfamerica.org/downloads/go13_consortium_modified_site_list.pdf

Lung Cancer Mutation Consortium. (2012, September 24). *About mutation testing*. Retrieved from Lung Cancer Mutation Consortium: http://www.golcmc.com/about-mutation-testing.html

Lynch, J. A. (2013, February 28). Utilization of epidermal growth factor receptor (EGFR) testing in the United States: a case study of T3 translational research. *Genetics in Medicine*, 1-9. doi:10.1038/gim.2013.5

Lynch, T. J. (2004). Activating mechanisms in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *The New England Journal of Medicine*, 2129-2138.

MacKinnon, N. a. (2001). Prior authorization programs: A critical review of the literature. *Journal of Managed Care Pharmacy*(7), 297-302. Retrieved from http://populationmedicine.net/content/pdf%5CAdams_JMCP_2001.pdf

Maemondo, M. I. (2010, June 24). Gefitinib or chemotherapy for non–small-lung cancer with mutated EGFR. *The New England Journal of Medicine, 362*(25), 2380-2388.

Maghfoor, I. P. (2010, September 27). *Non-small-cell lung cancer.* Retrieved from emedicinehealth: http://www.emedicinehealth.com/non-small-cell_lung_cancer/article_em.htm

Mahaney, F. X. (1989, September 20). Bone marrow transplants used against advanced breast. *Journal of the National Cancer Institute, 81*(18), pp. 1352-1353.

Maione, P. R. (2010). Advances in chemotherapy in advanced non-small-cell lung cancer. *Expert Opinion Pharmacotherapy, 11*(17), 1-11.

Majumdar, S. R. (2007). Impact of opinion leader-endorsed summaries on the quality of prescribing for patients with cardiovascular disease: a randomized controlled trial. *American Heart Journal, 153*(22), e1-e8.

Mandelblatt, J. a. (1995). Effectiveness of interventions to enhance physician screening for breast cancer. *Journal of Family Practice, 40*(2), 162-171.

Manolio, T. A. (2010). Genomewide association studies and assessment of the risk of disease. *The New England Journal of Medicine, 363*(2), 166-176.

Mariotto, A. B. (2011). Projections of the cost of cancer care in the United States: 2010-2020. *Journal of the National Cancer Institute, 103*(2), 117-128. Retrieved September 25, 2011, from http://jnci.oxfordjournals.org.libproxy.lib.unc.edu/content/103/2/117.full.pdf+html

Mason, J. F. (2001, December 19). When is it cost effective to change the behavior of health professionals? *The Journal of the American Medical Association, 286*(23), 2988-2992. Retrieved from http://jama.jamanetwork.com.libproxy.lib.unc.edu/article.aspx?articleid=194485

Maugh, T. H. (1990, May 14). Breast cancer survival rate may double, study finds. *Los Angeles Times*, p. B2 (col. 1).

MAXQDA. (2013). *MAXQDA - Qualitative data analysis software*. Retrieved from MAXQDA: http://www.maxqda.com/

McDonald, C. J. (1976, December 9). Protocol-based computer reminders, the quality of care and the non-perfectibility of an. *The New England Journal of Medicine, 295*(24), 1351-1355. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJM197612092952405

MCOL. (n.d.). *Managed care fact sheets: Current national managed care enrollment*. Retrieved September 25, 2012, from MCOL: Your source for health care business information since 1995.

Medicaid.gov. (2012, September 9). *Federal Policy Guidelines.* Retrieved from Medicaid.gov Keeping America Healthy: http://www.medicaid.gov/Federal-Policy-Guidance/Federal-Policy-Guidance.html

Medicare.gov. (2012, September 24). *Get help paying costs*. Retrieved from Medicare.gov: http://www.medicare.gov/your-medicare-costs/help-paying-costs/get-help-paying-costs.html

Medline Plus. (2012, February 23). *Managed care*. Retrieved from Medline Plus, a service of the US National Library of Medicine, National Institutes of Health: http://www.nlm.nih.gov/medlineplus/managedcare.html

Medves, J. G. (2010). Systematic review of practice guideline dissemination and implementation strategies for health care teams and team-based practice. *International Journal of Evidence Based Healthcare, 8*(2), 79-89.

Mello, M. m. (2001). The controversy over high-dose chemotherapy with autologous bone marrow transplant for breast cancer. *Health Affairs, 20*(5), 101-117. Retrieved from http://content.healthaffairs.org/content/20/5/101.full.pdf+html

Mok, T. S. (2009, September 3). Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *The New England Journal of Medicine, 361*, 947-957.

Murdoch, D. &. (2008). Will targeted therapy hold its promise? An evidence based review. *Current Opinions in Oncology, 20*(1), 104-111.

National Cancer Institute. (2009, November 23). *NCI's clinical trials cooperative group program*. Retrieved from National Cancer Institute at the National Institutes of Health: http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group

National Cancer Institute. (2010, April 15). *Cancer Trends Progress Report – 2009/2010 Update, Cost of Cancer Care.* Retrieved from National Cancer Institute, National Institutes of Health: http://progressreport.cancer.gov/print-detail.asp?pid=1&did=2007&mid=vcol&chid=75&coid=726

National Cancer Institute. (2010, Dec 9). *Stages of Non-Small Cell Lung Cancer*. Retrieved from Non-Small Cell Lung Cancer Treatment (PDQ): http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/Patient/page2#Keypoint8

National Cancer Institute. (2011, June 14). *Key Points*. Retrieved from National Cancer Institutes at the National Institutes of Health: http://www.cancer.gov/cancertopics/factsheet/NCI/NCI

National Cancer Institute. (2011, June 23). *Non-small cell lung cancer stage IV NSCLC treatment*. Retrieved from National Cancer Institute: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page11

National Cancer Institute. (2012, June 13). *Cancer Control and Comparative Effectiveness Research*. Retrieved from National Cancer Institute: http://cancercontrol.cancer.gov/cer/cer_funding.html

National Cancer Institute. (2012, December 5). *FactSheet Targeted cancer therapies*. Retrieved from National Cancer Institute: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted

National Cancer Institute. (2012, August 29). *Treatment options by stage*. Retrieved from National Cancer Institute: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/Patient/page5

National Cancer Institute. (2013, February 17). *Clinical trial search results*. Retrieved from National Cancer Institute: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=10931868

National Cancer Institute. (2013, March 20). *General information about non-small cell lung cancer*. Retrieved from National Cancer Institute: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/Patient/page1

National Cancer Institute. (2013, February 14). *Non-small cell lung cancer treatment (PDQ®)*. Retrieved from http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/Page11#Section_48630

National Cancer Institute. (2013, February 14). *Stage IV NSCLC treatment*. Retrieved from National Cancer Institute: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page11#Section_48630

National Cancer Institute. (n.d.). *FY 2011 Research funding by cancer type*. Retrieved September 26, 2012, from National Cancer Institute: http://fundedresearch.cancer.gov/search/funded;jsessionid=B71FB95C21DBE74161E5E12A12068606?action=full&fy=PUB2011&type=site

National Cancer Institute. (n.d.). *FY2011 NCI funded research portfolio* . Retrieved September 25, 2012, from National Cancer Institute: http://fundedresearch.cancer.gov/search/SearchForm

National Cancer Institute Office of Cancer Genomics. (n.d.). *OCG's mission*. Retrieved September 25, 2012, from National Cancer Institute Office of Cancer Genomics: http://ocg.cancer.gov/

National Cancer Institute Office of Genomic Research. (2012, March). *Office of Cancer Genomics fact sheet.* Retrieved from National Cancer Institute Office of Genomic Research: http://ocg.cancer.gov/objects/pdfs/OCG_FactSheet-508.pdf

National Comprehensive Cancer Network. (2012). *NCCN Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer v. 3.2012.* Retrieved April 18, 2012, from National Comprehensive Cancer Network: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Human Genome Research Institute. (2012, September 11). *About NHGRI: A brief history and timeline*. Retrieved from National Human Genome Research Institute: http://www.genome.gov/10001763

National Human Genome Research Institute. (2012, July 17). *Cancer Genetics Branch*. Retrieved from National Human Genome Research Institute: http://www.genome.gov/10000012

National Human Genome Research Institute. (2012, February 18). *Genetic Information Non-Discrimination Act of 2008.* Retrieved from Genome.gov : http://www.genome.gov/10002328

National Institutes of Health. (2011, March 3). *Mission*. Retrieved from National Institutes of Health: http://www.nih.gov/about/mission.htm

National Institutes of Health. (2012, August 7). *About NIH*. Retrieved from National Institutes of Health: http://www.nih.gov/about/

National Institutes of Health. (2012, August 14). *Institutes, Centers and Offices*. Retrieved from National Institutes of Health: http://www.nih.gov/icd/

National Lung Cancer Partnership. (2012, September 23). *Lung Cancer Mutation Consortium*. Retrieved from National Lung Cancer Partnership Research. Awareness. Change.: http://www.nationallungcancerpartnership.org/lung-cancer-mutation-consortium/

National Lung Cancer Partnership. (2012, July 26). Molecular tumor testing: opportunities for the lung cancer community. Retrieved July 26, 2012, from http://www.nationallungcancerpartnership.org/images/uploads/files/tumor-testing-webinar-slides.pdf

Nierendgarten, M. B. (2010, June 21). African-American genetic mutations post Rx challenge. *Oncology News International, 19*(6). Retrieved from www.c ancernetwork.com

Nobelprize.org. (1986). *The Nobel Prize in Physiology or Medicine 1986 - Press Release.* Retrieved February 20, 2012, from The official site of the Nobel Prize: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1986/press.html

North Carolina Oncology Association. (2012, December 21). *North Carolina Oncology Association (NCOA) membership roster* . Retrieved from North Carolina Oncology Association: http://www.ncoa-northcarolina.com/

O'Brien, M. A.-J. (2008). *Educational outreach visits: effects on professional practice and healthcare outcomes (review).* The Cochrane Library. London: John Wiley and Sons, Ltd.

Office of Cancer Centers. (2012). *Map of Cancer Centers.* Retrieved April 22, 2012, from National Cancer Institute: http://cancercenters.cancer.gov/cancer_centers/map-cancer-centers2.html

Office of Public Health Genomics. (2012, June 4). *About Us.* Retrieved from CDC Centers for Disease Control and Prevention: http://www.cdc.gov/genomics/about/index.htm

Okon, T. a. (2012, February). Are we winning the war on cancer? *American Journal of Managed Care, 18*(Special Issue 1), SP10-SP11.

Oncology Nursing Society. (2012). *About ONS*. Retrieved from ONS: http://www.ons.org/about

Osarogiagbon, R. U. (2011, March). Causes and consequences of deviation from multidisciplinary care in thoracic oncology. *Journal of Thoracic Oncology, 6*(3), 510-516. doi:doi: 10.1097/JTO.0b013e31820b88a7

Oteria, A. C. (2009, December 4). A Case of Bullous Dermatitis Induced by Erlotinib. *The Oncologist*, 1201-1204. Retrieved from http://theoncologist.alphamedpress.org/content/14/12/1201.long

Oxman, A. D. (1995). No magic bullets - a systematic review of 102 trials of interventions to improve professional practice. *Canadian Medical Association Journal, 153*(10), 1423-1431.

Paez, J. J. (2004). EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*, 1497-1500.

Pantoja, T. R. (2009). *Manual paper reminders: effects on professional practice and health care outcomes (protocol).* The Cochrane Collaboration. London: John Wiley & Sons, Ltd. Retrieved from http://onlinelibrary.wiley.com.libproxy.lib.unc.edu/doi/10.1002/14651858.CD001174.pub2/pdf

Pao, W. L. (2005). Erlotinib in lung cancer. *The New England Journal of Medicine, 353*(16), 1739-1741.

Pao, W. M. (2004). EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proceedings from the National Academy of Sciences*, 13306-13311.

Patlak, M. N. (2011). *The National Cancer Policy Summit: Opportunities and Challenges in Cancer Research and Care: Workshop summary.* Washington, D.C.: The National Academies Press. Retrieved September 25, 2012, from http://books.nap.edu/openbook.php?record_id=13101&page=31

Pennell, N. (2010, Oct 10). *Introduction to Molecular Markers.* Retrieved from Cancer Grace: http://cancergrace.org/lung/2010/10/10/overview-of-molecular-markers-in-lung-cancer/#more-4742

Perez-Soler, R. (2009). Individualized therapy in non-small-cell lung cancer: future versus current clinical practice. *Oncogene, 28*, S38–S45.

Pfizer. (2012, February). *Xalkori complete prescribing information.* Retrieved from Pfizer for Oncology Specialists: http://labeling.pfizer.com/showlabeling.aspx?id=676

Pho, K. (2011, June 5). *Advances in cancer treatment are hyped by headlines.* Retrieved from MedPageToday's KevinMD.com: http://www.kevinmd.com/blog/2011/07/advances-cancer-treatment-hyped-headlines.html

Potetz, L. a. (2009, February). *Cancer and Medicare: A Chartbook.* Retrieved from Alliance for Health Reform: http://www.allhealth.org/briefingmaterials/CancerandMedicareChartbookFinalfulldocumentMarch11-1412.pdf

Printz, C. (2010, Jul 15). BATTLE to personalize lung cancer treatment. Novel clinical trial design and tissue gathering procedures drive biomarker discovery. *Cancer, 116*(14), 3307-3008.

Reck, M. v. (2010, October). Erlotinib in Advanced Non-small Cell Lung Cancer. Efficacy and Safety Findings of the Global Phase IV Tarceva Lung. *Journal of Thoracic Oncology , 5*(10), 1616-1622.

Reeves, S. Z. (2009). *Interprofessional education: effects on professional practice and health care outcomes (review).* London: John Wiley & Sons, Ltd.

Reid, S. (2010). Transcript: CMMI listening session. *Capital Reporting Company CMMI listening session 12-10-2010* (p. 19). Aurora, CO: Capital Reporting Company.

Riely, G. J. (2006). Update on epidermal growth factor receptor mutations in non-small cell lung cancer. *Clinical Cancer Research, 12*(24), 7232-7241.

Robinson, J. (. (2006, Sept/Oct). Insurer's strategies for managing the use and cost of biopharmaceuticals. *Health Affairs, 25*(5), 1205-1217.

Roila, F. (2004). Transferring scientific evidence to oncological practice: a trial on the impact of three different implementation strategies on antiemetic prescriptions. *Supportive Cancer Care*, 446-453.

Rowland, J. M. (2004, June 25). Cancer survivorship --- United States, 1971--2001. *MMWR, 53*(24), pp. 526-529. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5324a3.htm

Satterlee, W. G. (2008). Effective medical education: insights from the Cochrane Library. *Obstetrical and Gynecological Survey, 63*(5), 329-333.

Schuster, M. A. (2005). How good is the quality of health care in the US? *Milbank Quarterly, 83*(4), 843–895.

Scott, A. S. (2011). *The effect of financial incentives on the quality of health care provided by primary care physicians (Review).* The Cochrane Collaboration. London: John Wiley & Sons, Ltd. Retrieved from http://onlinelibrary.wiley.com.libproxy.lib.unc.edu/doi/10.1002/14651858.CD008451.pub2/pdf

Sequist, L. B. (2007). Molecular predictors of response to epidermal growth factor receptor antagonists in non-small-cell lung cancer. *Journal of Clinical Oncology, 25*(5), 587-595.

Sequist, L. V. (2008). EGFR tyrosine kinase inhibitors in lung cancer: an evolving story. *Annual Review of Medicine, 59,* 429-442.

Sharma, S. V. (2007). Epidermal growth factor receptor mutations in lung cancer. *Nature Rev Cancer*(7), 169-181.

Shepard, F. A. (2005). Erlotinib in advanced non-small-cell lung cancer. *New England Journal of Medicine*, 123-132.

Shepard, F. A. (2005). Erlotinib in previously treated non-small-cell lung cancer. *The New England Journal of Medicine, 353*(2), 123-132.

Shepard, F. A. (2011, July 20). Molecular selection trumps clinical selection. *Journal of Clinical Oncology, 29*(20), 2843-2844.

Shojania, K. G. (2009, January 10). The effects of on-screen, point of care computer reminders on processes and outcomes of care (review). *Cochrane Database of Systematic Reviews*(3). doi:10.1002/14651858.CD001096.pub2.

Shojania, K. G. (2011). *The effects of on-screen, point of care computer reminders on processes and outcomes of care (review).* The Cochrane Collaboration. London: John Wiley and Sons, Ltd. Retrieved from http://onlinelibrary.wiley.com.libproxy.lib.unc.edu/doi/10.1002/14651858.CD001096.pub2/abstract

Silvestri, G. A. (2005). Targeted therapy for the treatment of advanced non-small cell lung cancer: a review of the epidermal growth factor receptor antagonists. *Chest*(128), 3975-3984.

Snyder, M. G. (2012, February). Payer management of oncology gets serious: Health plans continue to seek methods to curtail cancer costs. *The American Journal of Managed Care, 18*(Special Issue 1), SP6-SP9.

Squires, S. (1989, December 26). Bone marrow transplants may help breast cancer. *Washington Post*, p. Z5.

Stuart, B. (1999). *Advanced cancer and comorbid conditions: Prognosis and treatment.* Retrieved from http://www.moffitt.org/CCJRoot/v6n2/article5.htm

Szilagyi, P. G. (2000, October 11). Effect of patient reminder/recall interventions on immunization rates: A review. *Journal of the American Medical Association, 284*(14), 1820-1827. Retrieved from http://jama.jamanetwork.com/article.aspx?articleid=193164

Tan, W. W. (2011, Sept 2). *Non-Small Cell Lung Cancer.* Retrieved from Medscape Reference Drugs, Diseases & Procedures: http://emedicine.medscape.com/article/279960-overview#aw2aab6b2b5aa

Tan, W. W. (2012, April 12). *Non-Small Cell Lung Cancer*. Retrieved April 22, 2012, from Mescape Reference: http://emedicine.medscape.com/article/279960-overview#a0104

The American Journal of Managed Care. (2012, February). Where are we spending the most money in metastatic lung cancer? *The American Journal of Managed Care, 18*(Special Issue 1), SP36. Retrieved from http://www.ajmc.com/publications/evidence-based-oncology/2012/2012-2-vol18-n1/Latest-in-Literature

The Biomarkers Consortium. (2012, September 15). *Active projects*. Retrieved from The Biomarkers Consortium: http://www.biomarkersconsortium.org/projects_active.php

The Henry J. Kaiser Family Foundation. (n.d.). *Total Medicare Advantage enrollment, 2011*. Retrieved September 25, 2012, from The Henry j. Kaiser Family Foundation statehealthfacts.org: http://www.statehealthfacts.org/comparetable.jsp?ind=327&cat=6

The Italian Group for Antiemetic Research. (1998). Transferability to clinical practice of the results of controlled clinical trials: the case of antiemetic prophylactic treatment for cancer chemotherapy-induced nausea and vomiting. . *Annals of Oncology*, 759-765.

The Lung Cancer Mutation Consortium. (2012, September 24). *Welcome!* Retrieved from The Lung Cancer Mutation Consortium: http://www.golcmc.com/

The Zitter Group. (2012, April 27). *Expansion of prior authorization policies for oncology agents: Facing new agents and rising costs, payers continue to tighten their management of oncology.* Retrieved September 25, 2012, from The Zitter Group strategic solutions for managed markets: http://www.zitter.com/download/Expansion%20of%20Prior%20Authorization%20Policies%20for%20Oncology%20Agents.pdf

Travis, W. D. (2011, February). International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *Journal of Thoracic Oncology, 6*(2), 244-285.

Tsao, A. (2001, July 10). Cancer drugs the hype that dashes hope. *Bloomberg Businessweek.* Retrieved September 2, 2011, from http://www.businessweek.com/bwdaily/dnflash/jul2001/nf20010710_174.htm

Tsao, M. S. R. (2005). Erlotinib in lung cancer--molecular and clinical predictors of outcome. *The New England Journal of Medicine, 353*(2), 133-144.

U.S. Census Bureau. (2012, September 12). *Health insurance highlights: 2011*. Retrieved from Health insurance: http://www.census.gov/hhes/www/hlthins/data/incpovhlth/2011/highlights.html

U.S. Department of Health and Human Services. (2012, September 9). *About HHS.* Retrieved from HHS.gov US Department of Health and Human Services: http://www.hhs.gov/about/

U.S. Department of Health and Human Services. (2012, September 9). *The Department - FAQs.* Retrieved from HHS.gov US Department of Health and Human Services: http://answers.hhs.gov/categories/3

U.S. Food and Drug Administration. (2004, November 19). *FDA approves new drug for the most common type of lung cancer drug shows survival benefit.* Retrieved from US Food and Drug Administration: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108378.htm

U.S. Food and Drug Administration. (2012, December 17). *What does FDA do?* Retrieved from FDA US Food and Drug Administration Protecting and Promoting Your Health: http://www.fda.gov/aboutfda/transparency/basics/ucm194877.htm

Uramoto, H. &. (2007). Which biomarker predicts benefit from EGFR-TKI treatment for patients with lung cancer?. *British Journal of Cancer, 96*, 857-863.

U.S. News and World Report. (2014, January 6). *Oncologists*. Retrieved from Health Doctors: http://health.usnews.com/doctors/search?specialty=oncologists&gender=female

Wang, Y. S.-B. (2012, January 5). *Therapeutic advances in medical oncology. Erlotinib in the treatment of advanced non-small cell lung cancer. An update for clinicians.* Retrieved January 14, 2012, from Medscape: http://www.medscape.com/viewarticle/755979

WebMD. (2005, March 24). *Stages of Lung Cancer*. Retrieved from WebMD: http://www.webmd.com/lung-cancer/guide/stages-of-lung-cancer

Welch, H. G. (2002, May 4). Presumed benefit: lessons from the American experience with marrow transplantation for breast cancer. *BMJ, 324*, 1008. Retrieved from http://www.bmj.com.libproxy.lib.unc.edu/content/324/7345/1088

Wensing, M. a. (1994). Single and combined strategies for implementing changes in primary care: a literature review. *International Journal of Quality Health Care, 6*(2), 115-132.

West, J. H. (2010, May 22). *ASCO preview on TORCH trial: treatment order matters.* Retrieved from Cancer Grace: http://cancergrace.org/lung/2010/05/22/torch-trial-asco-preview/

West, J. H. (2010, July 8). *Changing practice in NSCLC: new research highlights value of early molecular testing.* Retrieved from Medscape: http://boards.medscape.com/forums?128@@.2a006730!comment=1

West, J. H. (2010, July 2). *Evidence that convinced me many people with advanced NSCLC should have up front molecular testing.* Retrieved from Cancer Grace: http://cancergrace.org/lung/2010/07/02/changing-clinical-practice-the-evidence-that-convinced-me-many-people-with-advanced-nsclc-should-have-up-front-molecular-testing/

Wisnivesky, J. P. (2011, July 14). Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: observational cohort study. *BMJ*, 1-10. doi:10.1136/bmj.d4013

Witt, K. &. (2008, September). (osi) pharmaceuticals and Genentec. *Important safety information*.

Wong, R. K. (2012). What is the best way to produce consensus and buy in to guidelines for rectal cancer? *Current Colorectal Cancer Reports*(8), 83-89. doi:DOI 10.1007/s11888-012-0121-x

Yamamoto, H. T. (2008, June 21). Impact of EGFR mutation analysis in non-small cell lung cancer. *Lung Cancer*, 3113-3120.