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Diffusion of the EGFR Assay: The Underutilization and the Urban/ Rural Divide

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DIFFUSION OF THE EGFR ASSAY: THE UNDERUTILIZATION AND THE URBAN/RURAL DIVIDE.

A Dissertation Presented

by

JULIE ANN LYNCH

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ABSTRACT

DIFFUSION OF THE EGFR ASSAY: THE UNDERUTILIZATION AND THE URBAN/RURAL DIVIDE

June 2012

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Purpose: The EGFR assay is a molecular diagnostic test which identifies a targetable mutation in lung tumors. Guidelines call for EGFR testing for non-small cell lung cancer patients to direct first line treatment. I explored institutional and regional factors predicting the likelihood acute care hospitals ordered the assay. Methods: This was a retrospective study which analyzed US acute care hospitals (n=4780). I linked proprietary industry data for orders of the EGFR assay to public datasets that provided hospital and regional characteristics. I conducted logistic regression to identify significant characteristics that predict likelihood a hospital ordered the assay. Results: Of acute care hospitals in the US, 12% (n=592) ordered the EGFR assay. In 49 counties with an NCI designated cancer center (NCI CC), 19% of hospitals ordered the assay. Hospital and regional characteristics had the hypothesized effect on likelihood a hospital would order the EGFR assay. Significant institutional predictors of ordering the assay included: Participation in an NCI clinical research cooperative group (odds ratio [OR], 2.06, 95% CI 1.66 to 2.55), Cardiothoracic Surgery (OR, 1.90; 95% CI, 1.52 to 2.37), PET Scan services (OR, 1.44, CI, 1.07 to 1.94), and affiliation with academic medical center (OR,

1.48; 95% CI, 1.20 to 1.83). Inpatient chemotherapy services were not statistically significant once all other institutional characteristics were stepped in. Significant regional predictors included: metropolitan county (OR, 2.08; 95% CI, 1.48 to 2.91), education above the mean (OR, 1.46; 95% CI, 1.09 to 1.96), and income above the mean (OR, 1.46; 95% CI, 1.09 to 1.96). Negative predictors were distance from an NCI CC (OR, .996, 95% CI, .995 to .998), a 34% decrease in likelihood for every 100 miles further from an NCI CC.

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CHAPTER 1

Purpose

The purpose of this thesis was to conduct an analysis of the diffusion of the epidermal growth factor receptor (EGFR) assay, a molecular diagnostic test designed to identify a specific somatic mutation in lung tumor tissue. The EGFR assay is an important innovation in the diagnosis and treatment of patients with non small cell lung cancer (NSCLC). Early identification of EGFR mutations in patients' lung tumors can improve the treatment and outcome for many such patients. The primary objectives of this analysis was to: 1) Identify institutional and regional factors that contributed to the adoption and utilization of the EGFR assay; 2) Elucidate structural factors that may contribute to differences in access to this technology; 3) Examine potential implications that differential rates of adoption have for poor patients living in rural counties; 4) Consider the role of nursing in administration, education, research, policy, and as patient advocate, to improve equity in access and utilization to advanced molecular diagnostic tests and to ensure implementation of evidence based clinical practice guidelines.

This was a retrospective, observational study using secondary data analysis research methods. The research was conducted on a national proprietary data set provided by Genzyme Genetics which identified institutions that ordered the EGFR assay for their patients in 2010. The proprietary dataset was merged with national, publicly available data sets including: Census Bureau Population Data (Census), National Institute of

Standards and Technology (NIST) county identification and location data, The National Program of Cancer Registries and Centers for Disease Control and Prevention (NPCR/CDC) State Cancer Profiles data, the 2009 Center for Medicare and Medicaid Services (CMS) and National Cancer Institute (NCI) Provider of Services institutional characteristics data (CMS/NCI POS).

The conceptual model that guided this research was based on four distinct bodies of literature:

(1) Clinical processes and guidelines for diagnosis and treatment of non small cell lung cancer
(2) Lung cancer disparities research
(3) Clinical trials of EGFR tyrosine kinase inhibitors (TKIs) and the EGFR assay
(4) Diffusion of innovation of healthcare services and technologies research

This literature helped generate the overall hypotheses that NCI designated cancer centers (CCs) serve as hubs from which diffusion of the EGFR assay emanates. The conceptual model was a two stage model. Stage one was a regional analysis with two dependent variables. The first dependent variable was the likelihood a county has an AMC that obtains designation from the NCI as a cancer center. The second dependent variable was the county utilization rate of the EGFR assay. Stage two of the conceptual model analyzed the likelihood individual institutions ordered at least one EGFR during the year 2010. The conceptual model proposes and tests two different measures of diffusion. One measure of diffusion was the county rate of utilization of the EGFR assay. It measured

the number of tests ordered within the county relative to the number of lung cancer cases in that county for which guidelines recommend testing. Throughout the thesis, this regional measure of diffusion will be called the utilization rate. The second measure of diffusion was the adoption of the EGFR assay by acute care hospitals within counties. In this paper, a hospital is considered to have adopted the EGFR assay if it ordered just one EGFR assay for a patient.

One of the limitations of this study was the lack of comprehensive information about the number of EGFR assays conducted by sixty clinical care NCI CCs. There were orders from twenty seven NCI CCs. However, many of these NCI CCs also conduct the EGFR assay independently. Therefore, all orders from NCI CCs were removed from the database. Given that limitation, the overall research hypothesis was utilization rate of the EGFR assay will be highest in counties in close proximity to NCI CCs, with the lack of information about NCI CC orders artificially suppressing the utilization rate within NCI CC counties, as well as for the entire United States (US).

The adoption of the EGFR assay, as measured by an institution ordering the assay, should be greatest among institutions that are either in close proximity to NCI CCs or that interact with NCI CCs through participation in cooperative clinical research groups. These institutions are also more likely to be affiliated with AMCs, early adopters of technology with the capabilities and equipment to offer advanced cancer care services, and located in metropolitan counties where the patient population has high income, education, and socioeconomic status. Institutions that are located in counties distant from

NCI CCs or are in rural counties that lack an NCI CC should be less likely to adopt the EGFR assay.

It was hoped that this analysis would shed light upon whether regional differences in access to molecular cancer diagnostics was a significant factor in the widening gap in quality and outcomes of healthcare services. Findings of this study will be used to inform a follow-up study which will examine patient level variables associated with access, adoption, and utilization of this healthcare innovation to determine whether barriers impact specific ethnic or racial groups.

Aims

The specific aims of this proposed study were:

(1) Create a dataset that links proprietary data provided by Genzyme Genetics, which identified institutions that ordered the EGFR assay for their patients in 2010, to several public use data sets. To achieve this aim, the following processes were conducted:

   a. Aggregated the individual orders for the EGFR assay to the institution and county level.
   b. Matched the institutional name listed in the Genzyme Genetics dataset to the name in the CMS/NCI POS datasets.
   c. Obtained CMS Oscar number for each institution that uniquely identified it.

d. Used the institution's zip code and county code to link and import proprietary and public datasets, which provide information about:

i. Characteristics of the acute care hospitals operating within the county.

(i) Annual lung cancer incidence and average annual number of lung cancer cases.

(ii) Population socioeconomic and demographic data of the county in which these hospitals are located.

(iii) Locational data that allows for geocoding and mapping of the institutions ordering the EGFR assay.

(2) Conducted exploratory analysis of the data to identify characteristics of the institutions and regions ordering the EGFR assays.

(3) Conduct descriptive and inferential statistical analysis of data.

a. Use descriptive statistics to summarize the independent variables that are associated with diffusion of the EGFR assay innovation.

b. Identify factors within specific counties that lead to healthcare institutions receiving the NCI designation.

c. Use logistic regression to analyze the odds ratio that a specific institution or county will have adopted the EGFR assay.

d. Use multiple regression analysis to calculate the strength of the causal relationship between the independent institutional and regional variables and EGFR assay utilization rate.

(4) Conclusions and implications that inform policy

Conceptual Modeling

The conceptual model that guides this research is based on four distinct bodies of literature:

(1) Clinical processes and guidelines for diagnosis and treatment of non small cell lung cancer

(2) Lung cancer disparities research

(3) Clinical trials of EGFR TKIs and the EGFR assay

(4) Diffusion of innovation of healthcare services and technologies research

A thorough review of the literature in each of these areas is conducted in Chapter 2. The discussion in this chapter is limited to a summary of the significant findings that informed the conceptual model and causal hypotheses.

Clinical processes and guidelines for diagnosis and treatment of NSCLC

Lung cancer treatment options are determined by stage of disease, performance status, tumor histology and presence of oncogenic mutations. NSCLC accounts for 85% of all lung cancers and adenocarcinomas represents 40% of NSCLC cases (Ettinger et al., 2010). Lung cancer is initially a silent disease which does not cause obvious signs or symptoms. In a small percentage of patients, early stage lung cancer may be discovered

accidentally through a chest x-ray related to another medical procedure or due to a coincidental, co-occurring respiratory infection. However, the majority of patients do not experience signs or symptoms of the disease until it has spread beyond the lungs and they are in the late stages of the disease process. For approximately 100,000 patients who have lung cancer, they will first experience vague respiratory symptoms which they, as well as their primary care provider, may suspect is either a viral or bacterial upper respiratory infection. Often, these symptoms are simply tolerated or treated with over the counter cough expectorants or suppressants. If symptoms persist, become worse, if a patient is coughing up blood (experiencing hemoptysis), or is in pain, these symptoms will encourage them to visit a hospital emergency room or their primary care physician. In both cases, the patient will likely have a chest x-ray. If a patient has respiratory symptoms and a suspicious mass is visible on a chest x-ray, clinical practice guidelines recommend the patient be referred to further imaging studies such as computerized tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography (PET) (Alberg, Ford, Samet, & American College of Chest Physicians, 2007). However, depending upon patient, institutional, and regional factors, the patient may or may not benefit from clinical practice guidelines. Patient factors that limit access to certain procedures include clinical symptoms, comorbid conditions, and sociodemographic factors. Institutional factors that may limit access are capabilities of the hospital or site of care and knowledge/expertise of providers. Regional factors that may limit access are physician practice patterns, availability and concentration of

healthcare providers and technologies, and population characteristics. All these are discussed in detail in Chapter 2 in the section of disparities in lung cancer treatment and outcomes.

Many patients die from lung cancer having only received a chest x-ray or an imaging study. Yet, conclusive diagnosis of lung cancer requires tumor tissue analysis. Health services researchers are discovering that clinical practice guidelines, like the EGFR assay, are a form of innovation that have differential rates of diffusion and which impact whether patients benefit from these guidelines. Assuming the patient benefits from clinical practice guidelines, when there is a suspicious finding on an imaging study, the patient should then be referred to an invasive procedure to extract tumor tissue. It is important to emphasize that conclusive diagnosis of NSCLC requires a pathologist to examine lung tissue under a microscope. Therefore, in theory, of the 222,000 patients who were diagnosed with lung cancer in the U.S. in 2010, approximately 68% (those with histology of non squamous cell NSCLC) should potentially have had access to the EGFR assay. However, the reality is that at any point in the clinical decision making process, large segments of the patient population are either denied access due to clinical reasons, institutional, or regional characteristics. Chapter 4 provides an analysis of the expected patient population that would have access to and utilize the EGFR assay.

Stage drives prognosis, treatment, and outcomes for patients with lung cancer. Although a detailed discussion of the treatment options in each stage are beyond the scope of this paper, it is important to understand the potential number of patients for

which tumor tissue extraction was realistically advisable and feasible. Generally, patients are eligible for surgical resection if they are diagnosed prior to stage IIIB when the cancer has spread to distant lung tissue or lymph nodes. Therefore, for approximately 100,000 patients in 2010 (those with Stage I to IIIA), surgical resection of the cancer may have been possible. Yet regardless of whether a patient is eligible for surgery, clinical practice guidelines recommend a tissue biopsy.

Depending upon location and accessibility of the suspicious mass, tissue biopsy could be performed by either bronchoscopy with transbronchial needle aspiration (TBNA), mediastinoscopy, endobronchial ultrasound-needle aspiration (EBUS-NA), endoscopic ultrasound-needle aspiration (EUS-NA), or transthoracic needle aspiration (TTNA) (Alberg et al., 2007). These guidelines recommend which procedure is best given clinical presentation, location of the tumor, and patient preferences. If a physician does not refer a patient to a procedure to conclusively diagnose lung cancer, that physician has impeded access to biopsy, surgery and the EGFR assay technology. In a few rare cases, the lack of referral may be clinically warranted due to debilitating coexisting medical conditions. If that physician refers the patient to surgery but the copayment prevents the patient from undergoing the procedure, health disparity researchers contend that socioeconomic factors have impeded access to both the surgery as well as the EGFR assay. If, on the other hand, the physician makes the referral and there are no financial or other structural barriers that impede access, yet the patient chooses non-treatment, then the patient had access but lacked utilization. The importance

of distinguishing between access and utilization may be unique to diffusion of healthcare services. It is particularly important to distinguish between these issues to elucidate causes of lung cancer disparities.

Disparities in lung cancer treatment and EGFR TKI clinical trials

Two decades of lung cancer disparities research illustrate racial, regional, and socioeconomic differences in access and utilization of bronchoscopy, surgical procedures, radiation therapy, chemotherapy clinical trials, and standard care (Greenwald, Polissar, Borgatta, McCorkle, & Goodman, 1998, Bach, Cramer, Warren, & Begg, 1999, Lathan, Neville, & Earle, 2006, Newman et al., 2004, Gross, Smith, Wolf, & Andersen, 2008). These finding were further reinforced by a systematic review conducted by the author of more than thirty-seven multicenter EGFR TKI and biomarker clinical trials that took place from 2001 until 2010. This review revealed that, of nearly 10,000 patients who participated in phase II and phase III EGFR TKI clinical trials, only 247 (3%) of patients who self identify as Black were enrolled in these studies. Similarly, there were only 219 (2%) patients who self identify as Hispanic. Institutions and patient groups that are most likely to utilize the EGFR assay are those who participated in and benefited from initial research studies to test the efficacy of this treatment relative to the standard of care. There is some overlap between findings in the EGFR TKI systematic review and the lung cancer disparities research. Both demonstrate a lack of participation among minority patient groups in standard care and clinical trial research.

Recent research by the Dartmouth Atlas Project indicate that geographic variation in the use of evidence-based medicine (EBM) is often even larger than racial disparities in care (Welch, Sharp, Gottlieb, Skinner, & Wennberg, 2011, Onega, Duell, Shi, Demidenko, & Goodman, 2010). Elucidating whether differences in access, utilization, and outcomes are caused by patient, providers, or structural factors is difficult. However, understanding these differences is fundamental to developing conclusive, clinically informed hypotheses about diffusion of the EGFR assay. Conclusions drawn from this research suggest that while socioeconomic and demographic variables such as race, income, and education, might be considered exogenous variables in empirical non-health services related research, these results call for their inclusion as endogenous variables in this causal model.

Diffusion of innovation

Roger's diffusion of innovation framework (1962) proposed three categories of variables that influence adoption and dissemination of new technologies: Characteristics of the social network; Attributes of the innovation; Aspects of the decision process (Rogers, 1962). Applying this framework to the EGFR assay informed the conceptual model in the following manner:

Characteristics of the social network

According to Rogers, healthcare providers' decision to use new products or change their practice patterns is strongly influenced by aspects of the professional social network in which they operate. He characterized the social network by existence of

opinion leaders, connectedness the members of the social network, their need for communication and their tolerance of risk. Analyzed in the context of adoption of the EGFR assay:

(1) Opinion leaders - Both the institution and healthcare providers that operate within the NCI CC serve as key opinion leaders with respect to the process of diffusion of the EGFR assay. Other institutions and healthcare providers that are within NCI CC network/communication channels are likely to be exposed to information about new technologies which are being developed and implemented in patient care at NCI CCs. Therefore these institutions adopt this technology sooner than healthcare providers operating at institutions distant to the NCI CC.

(2) Connectedness - The greater the number of NCI CCs and other hospitals affiliated with AMCs, the more network connectedness these oncologists have with oncologists operating in smaller community hospitals nearby.

(3) Members need for communication – Hospitals with an academic affiliation have a large number of young, transient medical staff and fellows working in their institutions who are linked by weaker social ties. When members of a group are transient, as occurs in AMCs with short term presence of residents, fellow, visiting faculty and physicians, there is a need to share information more frequently between members, which positively influences diffusion.

(4) Tolerance for risk - Healthcare providers working at hospitals with an academic affiliation and NCI CCs may be more tolerant of risk relative to their counterparts operating at small community hospitals that are distant from a population density. Tolerance of risk is influenced by age of residents and fellows, linkage to key opinion leaders, and knowledge about the science of the EGFR assay. Attendings and fellows operating within larger AMCs may be more insulated or protected from the risk of lack of financial reimbursement than permanent MDs operating within smaller community hospitals. The perception of lack of reimbursement may contribute to providers at community hospitals being more risk averse to adopting new technologies due to concern or lack of knowledge about reimbursement.

Attributes of the innovation

The ease and speed with which an innovation is taken up in the market is influenced by characteristics of the innovation and features of the product or service used in conjunction with, or in lieu of, the innovation. Rogers described these attributes as: relative advantage, compatibility, complexity, trialability, and observability (Rogers, 1962).

(1) Relative Advantage - When oncologists order the EGFR assay for a patient and an EGFR mutation is detected, the patient is often treated with an EGFR TKI in a first line setting. The oncologist then observes the benefit of knowing the mutational status. If the assay is not utilized, the patient may still receive

an EGFR TKI in the second or third line setting. Experience with an EGFR TKI has a positive influence on the diffusion of the EGFR assay. Oncologists who have not experienced (either directly or through their social network) the relative advantage of the EGFR assay to guide treatment, may perceive the relative advantage of the EGFR assay as less than their colleagues who have had experience with the assay. Therefore, both institutional and regional characteristics of the social network in which oncologists operate impact their perception of relative advantage of the EGFR assay. Oncologists who operate within a social network, in which opinion leaders have participated in the EGFR TKI clinical trials, will have directly or indirectly been exposed to the relative advantage of the EGFR assay. Experience with the EGFR assay and experience prescribing EGFR TKIs will increase the perception of the relative advantage and will increase adoption.

(2) Compatibility - Genetic analysis of tumor tissue began entering oncology practice in the mid 1990s with the treatment of Her2 positive breast cancers. For oncologists who operate within institutions that have the capability to provide advanced cancer care, adoption of the EGFR assay to identify the molecular biology of lung tumors will be consistent and compatible with other types of cancer care. One marker of an institution's capability to provide advanced cancer care may be utilization of other established cancer care technologies such as positron emission tomography (PET) scans technology.

(3) Complexity or simplicity - Genetic analysis of tumor tissue is a complex technology. However, the process of ordering the laboratory test from Genzyme Genetics is simple and routine. Institutions that participate in clinical research, offer advanced cancer care, and are classified as AMCs routinely send tumor tissue to outside labs for analysis. These institutions will perceive the EGFR assay as having less complexity. This will lead to faster adoption and diffusion of the technology within those institutions.

(4) Trialability - Institutional participation in clinical research provides MDs with the opportunity to trial the technology. Institutions that participate in an NCI clinical research cooperative group, or are identified as having an affiliation with an academic center are more likely to have trialed the EGFR assay and therefore adopt the technology.

(5) Observability - Although observability is not applicable to the EGFR assay, one might substitute whether the technology is easily identifiable to patient and physician groups. One barrier to diffusion of the EGFR assay is that lung cancer patients tend to be older and diagnosed at later stages. Therefore, the number of patients that can communicate about the technology to create visibility for the technology is limited compared to an assay used in diagnosis of cancers which are more chronic and less terminal, such as breast cancer. Although this attribute of the innovation certainly influences diffusion, there is no variable in our data that would measure observability.

Characteristics of the decision

Rogers also proposed that aspects of the decision to adopt innovation influenced diffusion. If the decision is optional, made by an individual rather than as a collective or in response to some authority or policy dictating it's use, then adoption is less likely to occur. These are discussed in the context of the characteristics of ordering the EGFR assay:

(1) Optional innovation decision - The decision to order the EGFR assay for a specific patient remains at the discretion of the individual physician, often an oncologist, surgeon, or pathologist.

(2) Collective innovation decision – Beginning in April 2010, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) called for use of the EGFR assay for diagnosis and treatment of specific lung cancer patients. Although clinical practice guidelines seek to improve translation of new technology into practice, the decision to follow the guidelines remains in the purview of the individual physician.

(3) Authority innovation decision - In countries with publicly funded health service systems, such as the United Kingdom, a government agency may issue guidelines for care or reimbursement that may essentially mimic an authority innovation-decision process. In the United States (US), such guidelines more often restrict the diffusion of a new medical technology rather than promote it.

> Currently, Medicare pays for reimbursement of the EGFR assay. However, Medicare policy does not ensure the physician has knowledge of that coverage. While reimbursement is not a significant barrier, particularly because the majority of patients diagnosed with lung cancer are over age sixty five and qualify for Medicare. Reimbursement did not result in the automatic adoption which might be observed in an authority-innovation decision process.

While the process of diffusion of innovation has been well researched in other markets, particularly consumer markets, only recently has it been applied to the healthcare services market. Few health disparity researchers applied the framework to analyze differences in access, utilization, and outcomes in healthcare. Roger's framework (1962) was a useful tool for articulating and categorizing variables within a causal model of diffusion. Yet, there are some important limitations worth noting. Rogers's model does not adequately address the barriers to diffusion that a complex regulatory and reimbursement environment can impose. Reimbursement of the EGFR assay is likely restricted by physician and institutional knowledge of how to bill for the assay. For institutions to receive adequate reimbursement, administrative billing or coding staff must have the knowledge and skills to accurately bill using several correct procedural terminal (CPT) codes. Frequently, billing and coding expertise is restricted by size and location of the institution. Although such expertise likely resides within large NCI CC or medical

centers with an academic affiliation, smaller community hospitals that have not been routinely obtaining genetic analysis of patient tumor tissue, might lack this expertise.

Roger's framework does not include cost in his discussion of attributes of the innovation. Particularly in the US healthcare system, there has been increased emphasis on the need to control the rising costs of healthcare. Providers are becoming increasingly aware of the cost of innovations and this may impede adoption and diffusion of the innovation.

Roger's framework also does not consider the timing and role of professional associations such as National Cancer Center Network (NCCN) or American Society of Clinical Oncology (ASCO) in their issuance of clinical practice guidelines. When there is a delay in the issuance of guidelines by such organizations, or when there is vacillation or uncertainty in the clinical utility of a health innovation, this confusion and uncertainty may significantly delay diffusion. The EGFR assay experienced both types of delays. There was confusion around the methodology for testing and whether patients lacking an EGFR mutation also benefited from and EGFR TKI. These were a factor in the pace of diffusion. In some cases, delays in diffusion may benefit patients by allowing better evidence to develop which may contradict the enthusiasm often generated from early results of innovation.

A recent review by Soleimani & Zenios (2011), suggested that the regulatory and reimbursement systems of the US contribute to incremental rather than disruptive approaches to innovation. They suggested that in some cases disruptive innovations may

have a greater impact on patient care. The framework by Christensen and Raynor (Christensen & Raynor, 2003) emphasized that while provider markets have seen disruptive innovation, patient markets have not. The example provided is the invention of cardiac stents, which essentially allowed interventional radiologists to compete with cardiac surgeons (Soleimani & Zenios, 2011). The innovation in the provider market increased competition for patients by two separate groups of providers competing for patients.

Lacking in the Soleimani & Zenios (2011) analysis is a discussion about the role principal-agent theory may have in the feasibility of disruptive innovations in patient markets. Principal-agent theory is an economic and legal concept in which a principal (the patient) delegates, either by choice or by necessity, authority to an agent (the physician) to make decisions about which healthcare services will be performed. This principal-agent theory is very applicable and relevant to the conceptual model of studying diffusion of the EGFR assay. As long as a physician referral/prescription is required to obtain access to and reimbursement for the EGFR assay, the physician and third party payer serve as gatekeepers to adoption, utilization, and successful diffusion of the EGFR assay. Whether physicians need to recommend patient access to the EGFR assay is in important consideration, one which will be taken up in the conclusion and implications section of this paper.

Given that diffusion of the EGFR assay is restricted by both patient choice and physician referral, which may be further restricted by institutional characteristics,

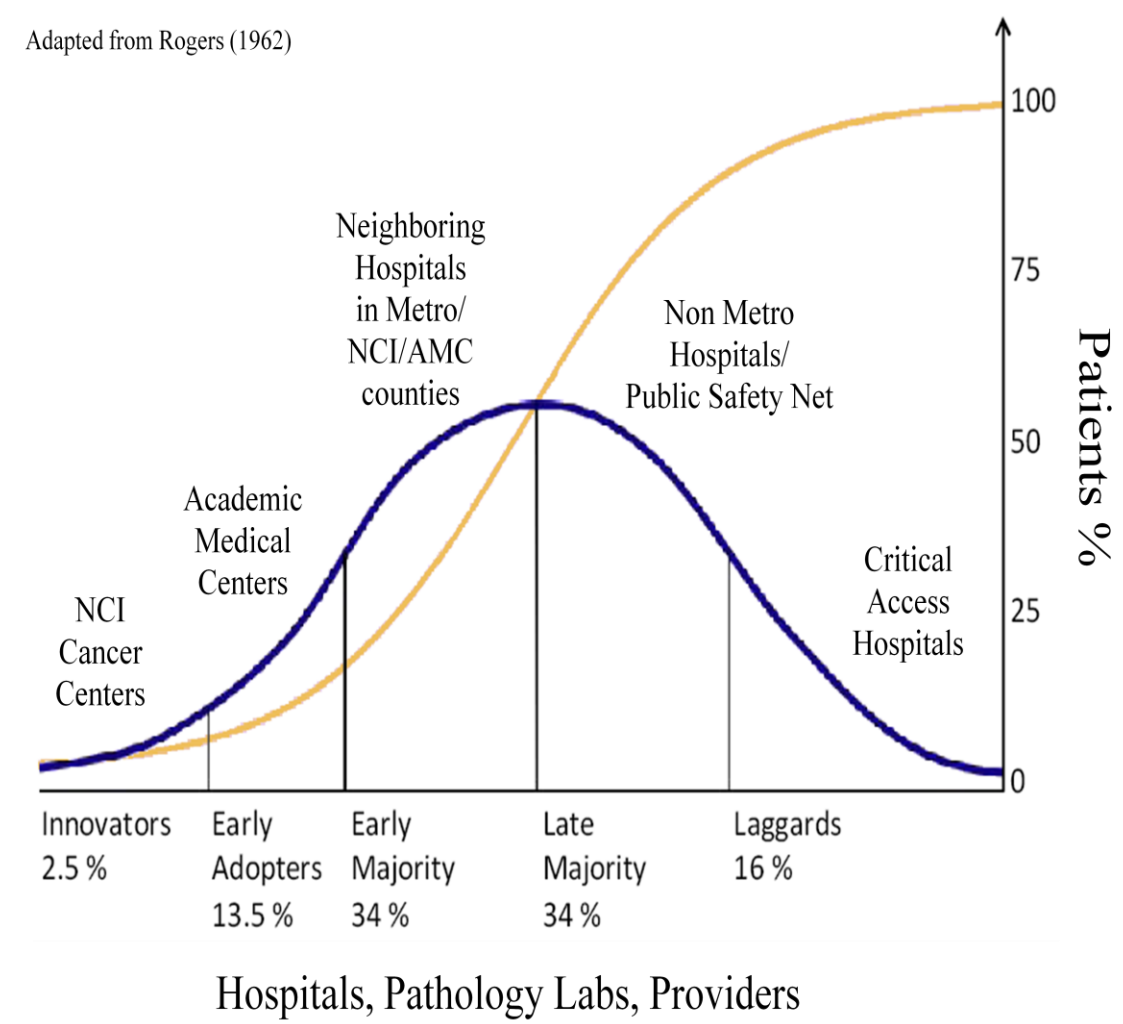
knowledge about reimbursement, or policies for implementing clinical practice guidelines, there are a few ways to measure successful diffusion of the EGFR assay. One measure of diffusion is the number of institutions that have adopted the assay. For purposes of this analysis, whether an institution has placed a single order for the EGFR assay for a patient in 2010 will be considered what Roger's diffusion theory calls adoption of that innovation (Rogers, 1962). Continued utilization and dissemination of the innovation is measured as the aggregated usage rate across institutions within each county relative to the annual number of lung cancer cases in that county that guidelines recommend receive the assay. That is defined as the utilization rate. For purposes of this analysis, the primary measures of diffusion are: whether institutions ordering the assay, the aggregated county level utilization rate, and the penetration rate, defined as the ratio of institutions ordering the assay relative to number of hospitals within county. These are defined in detail in Chapter 4.

Figures 1, 2, and 3 illustrate how significant findings of the literature were incorporated into Roger's diffusion of innovation theory. Figure 1 is the normal curve of distribution with adopters of innovation categorized according to Roger's theory. It illustrates my hypothesis of where in the process of diffusion hospitals fall based on institutional and regional characteristics. Consistent with the theory, the EGFR assay was developed by an NCI CC. Therefore, NCI CCs are in the innovator category. The academic medical centers (AMCs) which do not necessarily have NCI designation but participate in similar types of clinical cancer research are likely to be early adopters of

innovation. Neighboring hospitals in well educated, high income metropolitan counties surrounding the NCI CCs and large AMCs are likely to be in the early majority. Hospitals distant to the NCI CCs, located in non metropolitan counties, and categorized as critical access hospitals are expected to be within the late majority or laggards in adoption of innovation.

Figure 1

Proposed Categories of Adoption by Types of Acute Care Hospital



Notes: Illustrates the hypothesized impact that hospital and regional characteristics have on stage of adoption of new technologies
Source: Adapted from Rogers (1962)

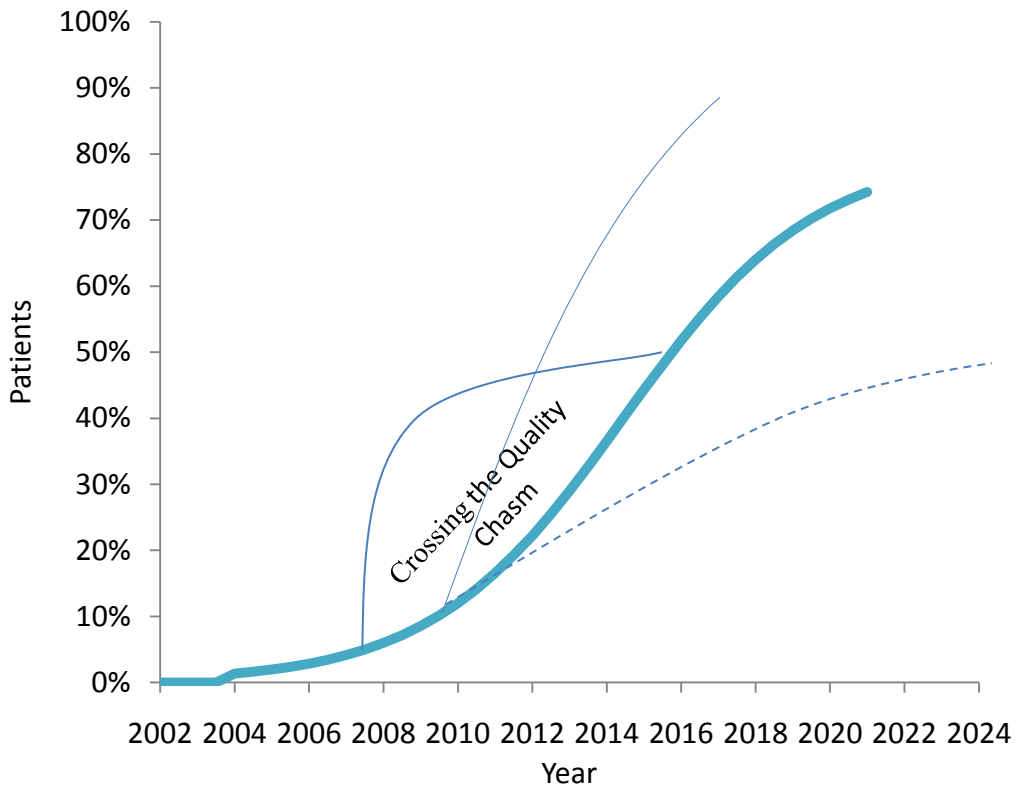
Figure 2 illustrates the raw data provided by Genzyme Genetics graphed using the logistic function to illustrate the s-curve of diffusion. The thick line is a forecast using the actual data from 2010. The parameters which determine the curve's shape are the date the innovation was introduced to the market and the date it reaches market saturation. The parameters used for this model were a 12.36% market penetration in year 2010 and by year 2018 it would reach market saturation with 80% of the eligible patients receiving the assay. This alpha value, which is the rate at which the function grows, is .30. The curve increases based on the expected number of adopters at each point. The inflection point is the year of greatest adoption, when the technology diffuses to greater than 50% of the population and the slope of the line moves toward 0. Several assumptions, upon which this graph is based, are debatable. However, the purpose is to illustrate the concepts of the adoption and diffusion curves.

The thin line shows the shape of the curve if healthcare providers were implementing evidenced based guidelines and recommending the assay to the majority of patients. The curve may peak in year 2014 when other technologies such as next generation sequencing platforms are developed. The dotted line shows the shape of the curve if there is continued lack of adherence to guidelines. This may happen if there was growing evidence that erlotinib was beneficial to all patients rather than just with those who have an EGFR mutation. Providers may then believe there is no use for the assay and continue to prescribe erlotinib in the second or third line.

Rogers often gets credit for the s-curve of diffusion but it was actually economist Ayers (1989) who illustrated that diffusion of innovation follows a logistic function S-curve. Rogers (1962) framework proposed that adopters of innovation fall along a normal distribution, which he categorized as innovators, early adopters, early majority, late majority and laggards. This curve also illustrates a concept which was popularized in healthcare by the Institute of Medicine (IOM) but which was originally proposed by Geoffrey A. Moore in his 1991 book entitled *Crossing the Chasm* (Moore, 1991). Moore analyzed adoption of information technology products. The IOM applied Moore's theories to analyze differences in the delivery of quality healthcare services. The IOM proposed that differences in quality exist due to delay in implementation of innovation and evidence based medicine to the overall population. The chasm refers to the time period between when the innovation is used by early adopters (which in my model would be the NCI CC and large AMCs) to when it is disseminated to the early majority. This time period coincides with the inflection point, which is halfway to market saturation. The number of adoptions per year peak at the inflection point and the slope of the diffusion curve moves toward 0. An important point is that Moore viewed this s-shaped curve as applicable to disruptive technologies which result in a significant change of behavior. There are many researchers which believe regulatory, reimbursement, and physician practices make disruptive innovations in healthcare difficult.

Figure 2

Diffusion of EGFR Testing Based on Genzyme Genetics Claims



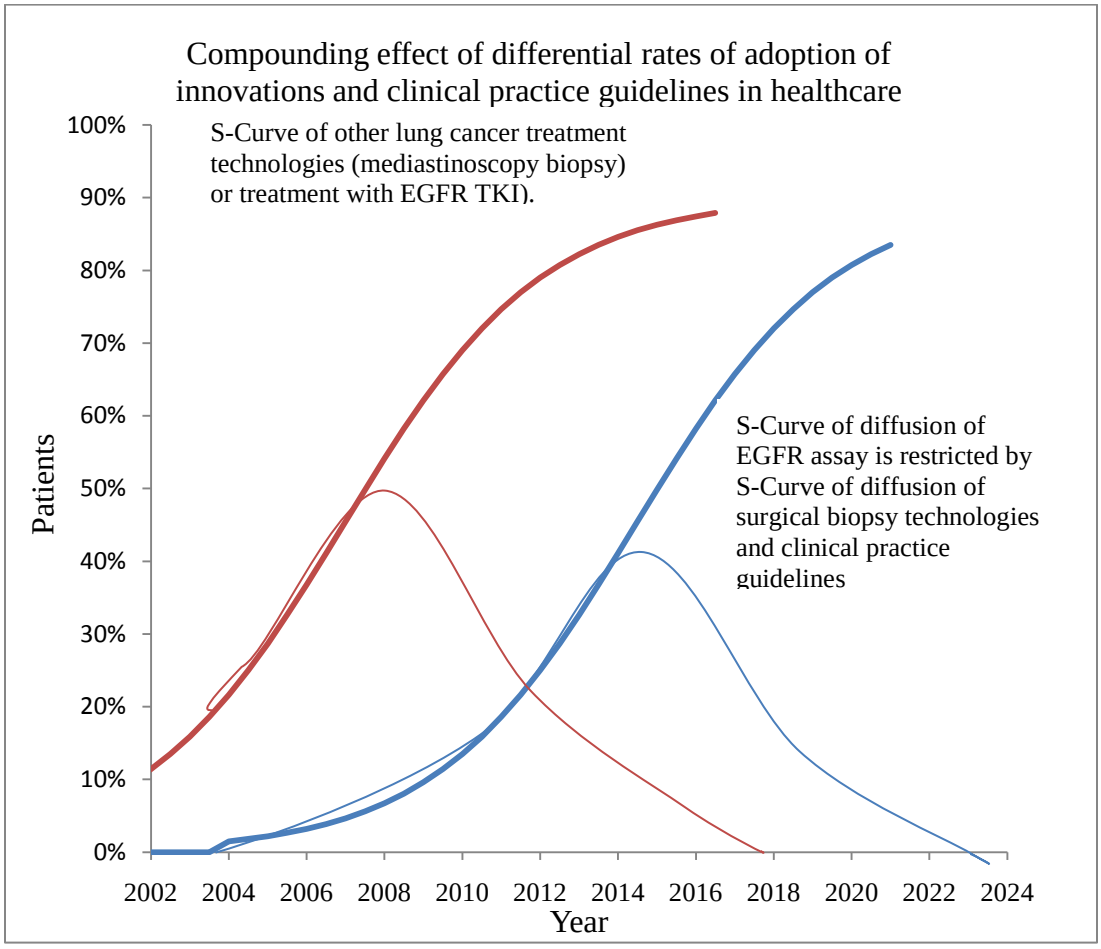
Notes: Thick line is logistic function assuming time 1 at 2010 of 12.36%, time 2 at 2018 at 80% and alpha .39. Thin line illustrates more rapid diffusion. Dotted line illustrates slower diffusion.
Source: Authors theoretical construction

In the discussion about lung cancer disparities research, one finding was that many lung cancer patients are denied access to evidenced based care that recommends patients undergo an invasive biopsy prior to diagnosis. I noted that if patients do not undergo an invasive biopsy to obtain tumor tissue, this compounds the disparity by

additionally preventing access to the EGFR assay. Figure 3 illustrates two hypothesized pairs of curves. The s-curves of diffusion that crosses the y axis at year 2002 with the adoption curve at 10% are for diffusion of the guideline recommending invasive biopsy to diagnosis lung cancer. The diffusion and adoptions curves to the right are for the EGFR assay. This illustration is meant to show how diffusion and adoption curves of the EGFR assay are restricted by the adoption and diffusion curves of invasive biopsies. According to these hypothesized curves, in 2010 only 70% of lung cancer patients underwent invasive biopsy. Therefore, only those patients would have access to the EGFR assay.

Figure 3

Compounding Effect of Differential Rates of Diffusion



Notes: Hypothesized diffusion and adoptions curves
Source: Author's theoretical construction

Assumptions of the conceptual model

The conceptual model assumes diffusion of the EGFR assay emanates from the NCI CC. Therefore, prior to analyzing the institutional and regional factors associated with adoption and diffusion of the EGFR assay, I analyze the regional factors associated with a county having an academic medical institution that obtains NCI designation. Having isolated those factors, I then measure the likelihood a hospital orders the EGFR

assay given its institutional and regional characteristics. Finally, I analyze the rate of use of the EGFR assay, calculated as the number of assays ordered in the county divided by the annual number of guidelines directed lung cancer cases in that county. Adoption is defined in this study as a hospital having ordered at least one EGFR assay from Genzyme Genetics. This analysis will be conducted at the institutional level and by whether the institution is located within the same county as an NCI CC. The county rate of utilization of the EGFR assay refers to the number of EGFR assays ordered relative to the number of lung cancer cases within the county. This analysis will also be conducted by whether there is an NCI CC within the county or not.

It is worth noting that county characteristics that positively influence the utilization rate in counties without an NCI CC, may, in some cases have the opposite effect in counties with an NCI CC. For example, the average age of diagnosis of lung cancer is age 71. Although patients under the age 45 can be diagnosed with lung cancer, the vast majority of patients are diagnosed after age 45. The lung cancer disparities research has revealed that patient populations most likely to undergo an invasive procedure to obtain tumor tissue or surgical resection are nonminority patients, with higher education and incomes. Therefore, metropolitan counties with urban centers have a high percentage of young minorities which positively influence the location of an NCI CC. Yet, those same characteristics may contribute to a lower utilization rate because young minorities are not often diagnosed with cancer.

The different dependent variables for each stage of the model are:

Table 1

Dependent Variable in Each Stage of the Conceptual Model

Equation	Dependent Variable	Measured
1	Is there an NCI CC in the county	0/1 - No/Yes
2	Did the hospital order the EGFR assay	0/1 - No/Yes
3	County EGFR adjusted utilization rate	0-1*

Notes: * Presumes assay is conducted during initial diagnosis rather than reflexive testing of patients diagnosed in prior years. Further presumes cross county utilization is limited.
Source: Author's construction

It is also necessary to explain that, although this study analyzes diffusion of the EGFR assay, the literature reviewed suggests persistent institutional and regional differences in patient access and utilization of older innovations and clinical practice guidelines in the treatment of lung cancer. These persistent differences in older technologies will also contribute to a slower rate of diffusion for the EGFR assay.

In the US healthcare system, current policy does not consider the cost benefit analysis of medical interventions. Therefore, in theory, all patients diagnosed with NSCLC, for whom guidelines recommend lung tumor genotyping, should have access to the EGFR assay. However, as described in Figures 2 and 3, if patients are not provided access to advanced technologies for conducting lung tumor tissue biopsy, such as mediastinoscopy, access to and diffusion of the EGFR assay is restricted. Further, if institutions have not been exposed to the benefits of treating patients with an EGFR TKI, they are less likely to understand the importance of conducting lung tumor genotyping. So, although in theory all guideline recommended NSCLC patients should have access to

the EGFR assay, the reality is that a large segments of the population will be denied access because they live in remote parts of the country that do not have acute care hospitals or because they obtain care at critical access hospitals (CAHs) that may not provide advanced cancer care services. Further, as many as 10% of the lung cancer patients offered biopsy or surgery refuse to undergo these invasive procedures. Table 2 provides a reasonable estimate of the 2010 population that could have had access to the EGFR assay.

Table 2

Estimate of Patient Population that Could Access to the EGFR Assay	CDC/NPCR
Number of incident lung cancer cases in 2010	208,603
NSCLC is 85% of lung cancers	177,313
Routine testing for squamous cell not recommended	(35,463)
Guideline recommended testable population	141,850
Patients in 503 counties that have no acute care hospitals	(7,403)
10% of patients offered biopsy or surgery for lung cancer refuse	(20,860)
Estimate of 2010 testable population	113,587

Notes: Incidence number derived from the National Program of Cancer Registries (NPCR) and Centers for Disease Control and Prevention (CDC) State Cancer Profiles in 2011.
Source: Author's construction

With a testable population of 113,587 and Medicare paying between $622.58 and $836.01 per test, it would cost the country approximately $70 million dollars a year to test all guideline directed lung cancer patients for an EGFR mutation. Most of these patients are over age 65, which generates debate about whether genomic analysis of all these patients is a cost effective intervention. In countries with publicly funded national

medical care, medical interventions must meet a maximum threshold of cost per life year saved. There is considerable debate in the US whether the rising cost of healthcare as a percentage of growth domestic product will require a similar cost benefit analysis of medical interventions be implemented in this country. The cost effectiveness of molecular diagnostics such as the EGFR assay is achieved by identifying the specific segment of the population that will benefit from the targeted therapy. In an environment in which the EGFR assay is not used, the EGFR TKI is often prescribed to patients that will achieve no benefit. The cost of erlotinib is approximately $2000 per month, more than twice the cost of the EGFR assay. If all 113,587 guideline directed lung cancer patients were being prescribed erlotinib for one month, this would cost the government approximately $227 million. If only the 15% of patients with an EGFR mutation were being prescribed erlotinib, this would cost the government $34 million. Therefore, the cost effectiveness of the EGFR assay, and many other molecular diagnostics identifying somatic mutations, is in cost savings that could potentially be achieved from limiting access to molecularly targeted drugs. However, the US healthcare system has, to date, not restricted access to medical interventions based on cost or comparative effectiveness analysis.

As discussed previously, a limitation of the dataset is incomplete information on the NCI CC utilization of the EGFR assay. Twenty seven NCI CCs had ordered EGFR assays through Genzyme Genetics in 2010. However communication with some of these centers confirmed that the EGFR assay is often conducted within the NCI CC's own lab

as part of a clinical trial protocol. According to Genzyme Genetics, it contracted with four of the large, well established NCI CCs for whom it conducted the EGFR assay exclusively. Information on the utilization within these NCI CCs was extrapolated to impute an estimate of overall utilization by NCI CCs. Table 3 provides an estimate of the NCI CC utilization. The estimate was based on the actual usage by four NCI CCs. These NCI CCs had contracted with Genzyme Genetics to be the exclusive provider of the EGFR assay. The utilization rate for these NCI CCs was between 15 and 50% of their annual lung cancer incidence. Therefore, we assumed that NCI CCs conduct EGFR assays on 30% of their county's annual lung cancer cases.

Table 3

Estimate of Number of EGFR Assays Conducted at NCI CCs

Number of annual lung cancer cases in 49 NCI counties	23,680
Genzyme Genetics database has complete information on 4 NCI CCs. These 4 centers have a utilization rate between 15%-50% of their counties annual lung cancer cases. So, let's assume NCI CCs have 30% utilization rate	7,104

Notes: Formula for imputed estimate: Summarize guidelines directed lung cancer cases in 49 NCI counties and multiply by .30. Does not consider extensive border crossing that is likely taking place by patients outside of NCI counties seeking care within NCI CCs.
Source: Author's theoretical construction

Table 3 suggests that use of the EGFR assay by the 62 comprehensive cancer centers exceeds use nationally by the 4,720 other acute care hospitals included in the database. While this underscores the limitations in the dataset, it also suggests significant underutilization of the assay. Table 4 provides an estimate of overall diffusion rate of the

EGFR assay for 2010. This rate was calculated by taking the actual orders of the EGFR assay by non-NCI institutions and adding the imputed estimate of use by NCI CCs.

Table 4

Estimate of US Diffusion Rate of the EGFR Assay

Actual utilization from Genzyme Genetics database excluding NCI CCs	6,936
Estimated NCI CC utilization	7,104
Proposed 2010 testable population (market size)	113,587
Utilization rate = Number of tests/number of cancer cases	12.36%

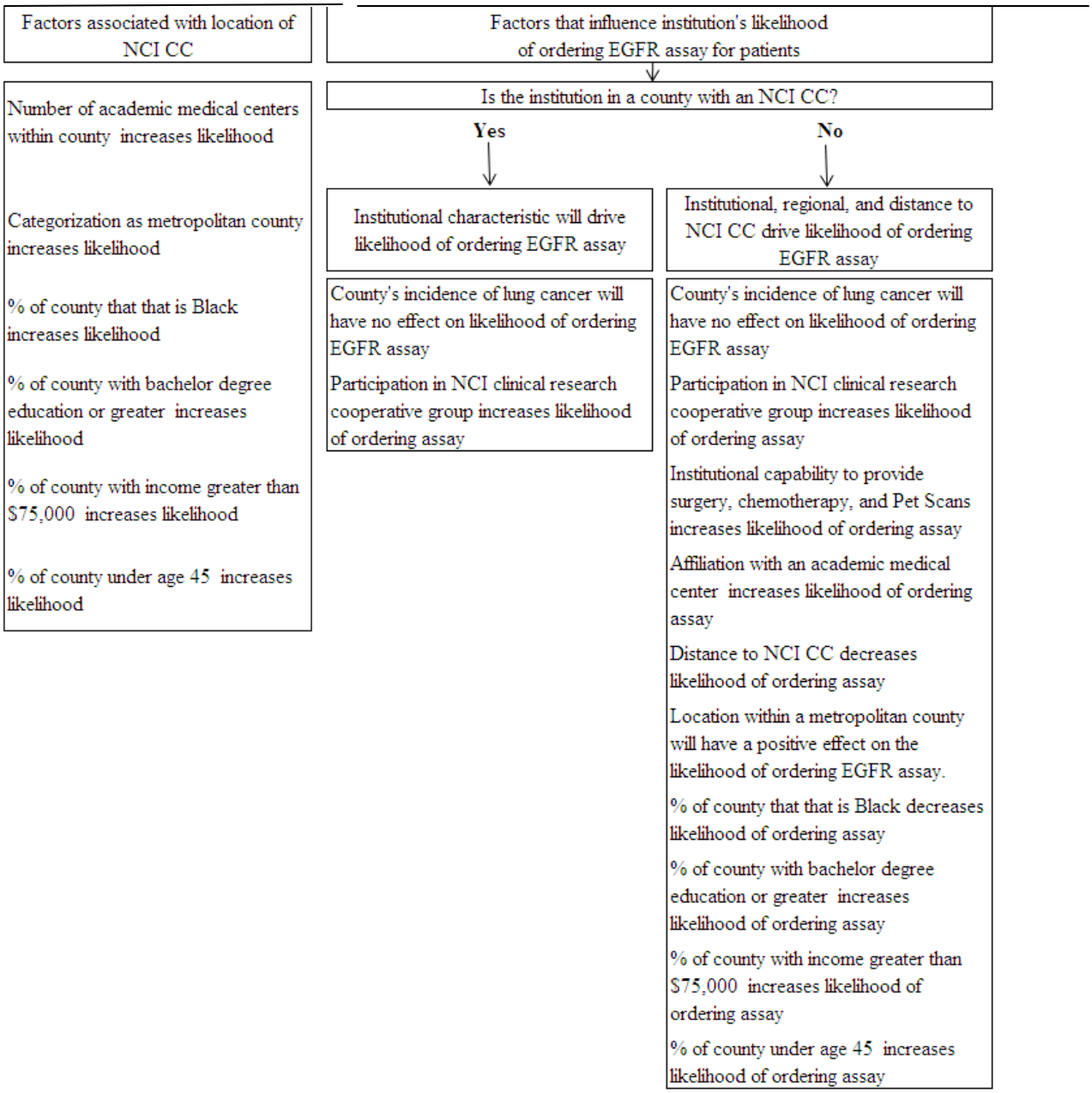
Notes: Estimated rate based on incidence rate in one year. Does not include reflexive testing for prior years.
Source: Author's theoretical construction

This information makes it possible to illustrate how Rogers (1962) theory of diffusion informed the conceptual model analyzing adoption and utilization of the EGFR assay.

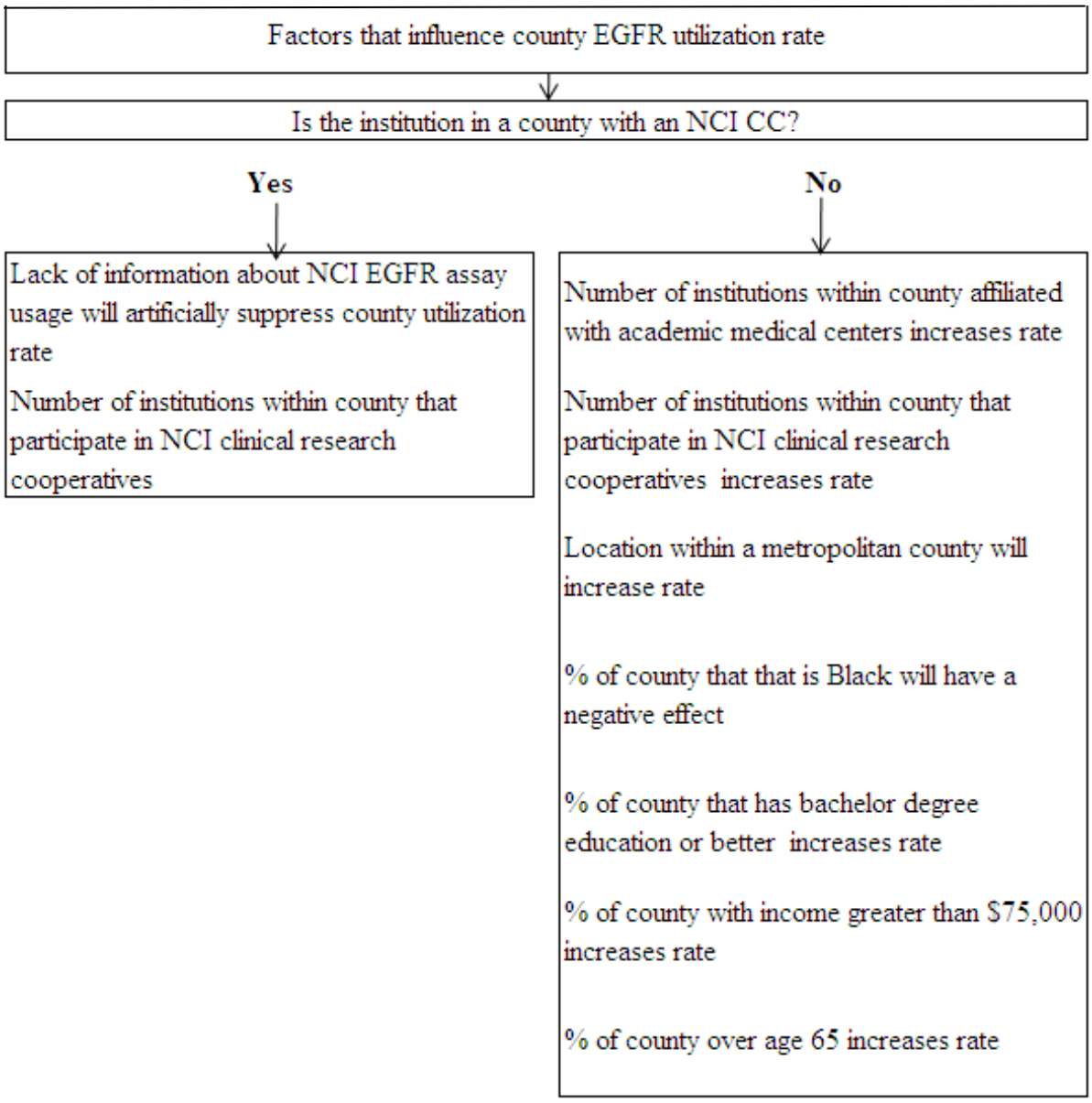
Illustration of the Conceptual Model

Figure 4 provides an illustration of the conceptual model. It is a two step approach with two measures of diffusion. The first measure of diffusion is adoption of the assay by acute care hospitals. The second measure of diffusion is the county EGFR utilization rate.

Figure 4
Steps in the Conceptual Model



Equation 3


Factors that influence county EGFR utilization rate
Is the institution in a county with an NCI CC?
Yes
No
Lack of information about NCI EGFR assay usage will artificially suppress county utilization rate
Number of institutions within county that participate in NCI clinical research cooperatives
Number of institutions within county affiliated with academic medical centers increases rate
Number of institutions within county that participate in NCI clinical research cooperatives increases rate
Location within a metropolitan county will increase rate
% of county that that is Black will have a negative effect
% of county that has bachelor degree education or better increases rate
% of county with income greater than $75,000 increases rate
% of county over age 65 increases rate

Hypotheses

Most patients diagnosed with NSCLC are over age 65. Therefore, in a rational, equitable healthcare system, in which Medicare coverage reduces reimbursement barriers, the majority of NSCLC patients should receive quality medical care that is guided by the evidence reflected in clinical practice guidelines. Only a patient's inability or unwillingness to pay the coinsurance or undergo an invasive tumor biopsy should restrict access to the EGFR assay. A review of the literature discussed within Chapter 2 suggests that whatever the research hypotheses listed below, the probability that the null hypothesis is correct is very low.

Equation 1 hypotheses – Analysis of location of NCI CC

As mentioned earlier, a key assumption of this conceptual model is that diffusion of the EGFR assay emanates from the NCI CCs. Therefore, it is important to understand the regional factors associated with an academic medical center obtaining NCI designation.

(1) Number of institutions within county affiliated with AMCs will have a positive effect on the likelihood there is an NCI CC within the county.

(2) Metropolitan categorization will have a positive effect on the likelihood there is an NCI CC within the county.

(3) Percentage of the county population that self identify as Black will have a positive effect on the likelihood there is an NCI CC within the county.

(4) Percentage of the county population with education of a bachelor's degree or greater will have a positive effect on the likelihood there is an NCI CC within the county.

(5) Percentage of the county population with income greater than $75,000 will have a positive effect on the likelihood there is an NCI CC within the county.

(6) Percentage of the county population under age 45 will have a positive effect on the likelihood there is an NCI CC within the county.

Equation 2 hypotheses – Likelihood any U.S hospital ordered EGFR assay

As discussed in the introductory pages, it is believed that presence of an NCI CC in the county has a significant influence on the likelihood an institution will order an EGFR assay. Therefore, the institutional and regional analysis will be conducted with NCI county as one causal factor. It should also be noted that the 60 clinical care NCI CCs are located within 49 counties. Institutional hypotheses are:

(1) Annual cases of lung cancer within the county will raise the likelihood of institutions ordering an EGFR assay.

(2) Whether an NCI CC is present in the county or not, participation in an NCI clinical research cooperative group has a positive influence on the likelihood it orders the EGFR assay.

(3) Institutional capabilities to provide cardiothoracic surgery, chemotherapy and advanced imaging (Pet Scan) increase the likelihood it orders the EGFR assay.

(4) Affiliation with an AMC has a positive influence on likelihood it orders the EGFR assay.

(5) Distance between the hospital and NCI CC will have an inverse relationship to the likelihood the institution orders the EGFR assay.

(6) Location within a metropolitan county will have a positive effect on the likelihood of ordering EGFR assay.

(7) Within non NCI CC counties, the percentage of the population that is Black will have a negative effect on the likelihood the institution adopts the EGFR assay.

(8) Institutions located in counties in which there is a large percentage of the population with education of a bachelor's degree or greater, will have a positive effect on the likelihood it orders the EGFR assay.

(9) Institutions located in counties in which there is a large percentage of the population with income above $75K will have a higher likelihood it ordered the EGFR assay.

Equation 3 hypotheses – Regional factors influencing EGFR utilization rate

(1) NCI CC within county will suppress EGFR Presence of NCI CC in county will suppress EGFR utilization rate due to lack of NCI CC data

(2) Whether an NCI CC is present in the county or not, number of institutions within a county participating in NCI cooperative clinical research groups will have a positive effect on the rate of EGFR assay utilization.

(3) Number of institutions within county affiliated with AMCs will increase rate of EGFR assay utilization

(4) In non NCI counties, location within a metropolitan county will increase rate of EGFR assay utilization.

(5) In non NCI counties, the percentage of the population that is Black will have a negative effect on the rate of EGFR assay utilization.

(6) In non NCI counties, the percentage of the population with education of a bachelor or greater will have a positive effect on the rate of EGFR assay utilization.

(7) In non NCI counties, the percentage of the population with Income greater than $75,000 will have a positive effect on the rate of EGFR assay utilization.

(8) In non NCI counties, the percentage of the population that is under 45 will have a positive effect on the rate of EGFR assay utilization.

Significance

This dissertation research is significant from a number of different perspectives: Studying differential rates of access to lung tumor genotyping may elucidate factors that have contributed to persistent socioeconomic and structural differences in diagnosis, treatment, and outcomes in lung cancer. Identifying barriers that exist in access to the EGFR assay may help inform the implementation of evidence based clinical practice guidelines and translational research in other areas of health innovation. Nurses, as administrators, clinicians, educators, policy analysts, and researchers, are on the forefront

of implementing healthcare innovations. Understanding the process of diffusion is a critical component to successful dissemination of innovation. Further, the nursing discipline itself is currently undergoing significant change and innovation within its own professional practice. Analyzing diffusion of a cancer diagnostic technology will inform nurse researchers of the tools required to successfully implement, measure, and monitor the dissemination of innovations within the nursing discipline.

Contexts

This section establishes the background in which this research question was generated. It provides a brief overview of the development, commercialization, and licensing of the EGFR assay. Further, it provides the traditional health policy framework analysis of the historical, political, sociological, economic perspectives of the federal government's role in the development and funding of cancer diagnostic and treatment technologies clinical trials.

Background on development of the research question

The impetus for this research study was generated in 2007 when the Director of Equity at Dana Farber Cancer Institution and Harvard Comprehensive Cancer Center (DF/HCC) described a growing perception among thoracic oncologists that erlotinib was not as effective in Blacks as it was in Whites due to a lower incidence of EGFR mutations in Black lung cancer patients. At the time, there was one paper published which had oversampled Blacks to get 50 patients in study who self identified as Black. It reported an incidence rate of EGFR mutations in Blacks as 2.4% or 1 patient (Yang et al.,

2005). Being familiar with the well established research documenting the problems of under representation of minorities in cancer clinical trials and at NCI CCs, I questioned whether there was enough evidence in the EGFR TKI clinical trials to substantiate the belief that EGFR mutations in Blacks is rare. In effort to investigate this, I contacted several leading thoracic oncology principal investigators at NCI CCs to request information about the number of Blacks enrolled in EGFR TKI clinical trials and biomarker studies. Five of the country's leading thoracic oncologists, who were also active principal investigators in the EGFR TKI clinical trials, reported that few Blacks were enrolled in the EGFR TKI treatment or biomarker clinical trials. The student researcher then questioned whether there was also under representation of lung tumor tissue from Blacks in tissue banks. Pathologists responsible for overseeing large NCI funded lung tumor tissue banks reported that only recently had tissue banks begun to record ethnicity and race of patients' tumor tissue in their anonymous tissue bank. From this limited qualitative/investigational approach, the student developed her main research interest which was investigating whether the patterns of enrollment of patients in lung cancer clinical trials contributes to growing gap in lung cancer outcomes among poor and minority patients.

Development, commercialization, and licensing of the EGFR assay

In April 2004, two research groups at the federally funded NCI CC, DF/HCC, proved the link between clinical responsiveness to an EGFR TKI and a mutation in the EGFR receptor (Lynch et al., 2004; Paez et al., 2004). This discovery lead to the

development of the EGFR assay. By September 2005, DF/HCC and its investigators sold the worldwide rights to market and distribute the EGFR assay to Genzyme Genetics (Genzyme Genetics, 2005). In February 2008, Genzyme Genetics sublicensed the worldwide rights, with the exception of North America and Hong Kong, to DxS, a company based in the UK. This company, in collaboration with Astra Zeneca, had developed and was marketing its own version of the EGFR assay (Genzyme Genetics, 2008) and was marketing it in Europe for use as a companion diagnostic in combination with Astra Zeneca's EGFR TKI gefitinib. In 2009, Genzyme Genetics expanded the license with DxS to include the US market. However, during this time, DxS was in a dispute with Roche Diagnostics over the rights to its EGFR mutation detection kid. Further, DxS was in the process of being acquired by a larger UK based company, Qiagen. Therefore, DxS's focus on the marketing and distribution of the EGFR assay in US was minimal. According to Genzyme Genetics, the agreement with DxS did not make any meaningful contribution to the number of EGFR assays sold in the US market. By late November 2010, Roche Diagnostics, one of the largest, publically traded diagnostic and pharmaceutical companies in the world, also sublicensed from Genzyme Genetics, the worldwide rights to market and distribute the EGFR assay. Following this transaction, LabCorp, a large, publically traded clinical research organization, announced its intention to acquire Genzyme Genetics.

Frequent licensing, acquisitions, and merger activity is common for companies and technologies that are early in the s-shaped diffusion curve, particularly when there is

a belief or perception that the slope of the curve is about to increase rapidly. Such commercialization may also lead to better access for poor and minority patients because diffusion of the innovation may become disruptive rather than the slower, incremental approach that takes place in the initial stages of federally funded translational research.

An important question health service researchers need to consider is, given that many innovations in cancer treatment are developed by institutions supported by federal taxpayer funds, whose responsibility is it to ensure that: 1) Development of health innovations are informed by diverse patient populations. 2) Minority and poor patients achieve the same timely benefit from health innovations as patients who routinely seek care at the institutions developing these innovations. The following section discussed the federal government's investment and commitment to these issues.

Federal government's sponsorship of cancer clinical research

Historically, the federal government has provided substantial financial and political support for cancer research and care. This support began with the 1930 passage of the Ransdell Act creating the National Institute of Health (NIH), authorizing the establishment of fellowships for research into basic biological and medical problems, and regulating new drug development (Starr, 1982). In 1937, Congress authorized the creation of the NCI along with Public Health Service, which funded cancer research in both its own labs as well as outside labs. Ten years later, NCI reorganized to provide an expanded program of intramural cancer research, grants, and cancer control activities with appropriations to the states and AMCs for their support of cancer control activities.

The investment and coordination from the Federal Government in clinical research catapulted clinical trials to a new level. Indeed some researchers cite the 1940s through the 1960s as the golden years of clinical research (Swazey & Fox, 2004). Involvement by the federal government enabled the development of large scale clinical trials across geographically diverse populations. By 1954, NCI established a full-scale clinical research program through sponsorship of multicenter clinical trials cooperative groups, of which the leading academic research centers were members. The following year, NCI organized the first solid cancer cooperative group, the Easter Cooperative Oncology Group (ECOG), which became the largest cooperative group consisting of 4000 members. By 1960, most phase II and phase III clinical cancer trials were devised and administered by the NCI. By 2000, there were more than 10,000 investigators and 3,000 institutions registered with NCI (Keating & Cambrosio, 2002).

The rise of evidenced based medicine (EBM) has elevated the recognition and use of clinical research to a prominent level in healthcare. Randomized control trials (RCT) are now considered the gold standard in the hierarchical evaluation of clinical evidence.

Despite the significant federal investment and rapid expansion of clinical research, throughout the 1980s and 1990s, there was a lack of minority and elderly participation in cancer clinical trials. In 1993, the NIH, recognizing failures in the healthcare system to provide access for women and minorities to clinical research, established the Revitalization Act of 1993. This Act was mandated by Congress in Section 492B of Public Law 103-43. Congress sought to establish an ethical principal of

justice, emphasizing the importance of balancing the burden of research with its benefits (NIH, 2008). Prior to enactment of the NIH inclusion policy, several incidents of unethical treatment of patients in clinical research, most notably the Tuskegee syphilis trials that took place from 1932 until 1972, and the 1977 thalidomide trials in pregnant women, resulted in researchers becoming overly cautious about recruiting minorities and women in clinical research (Killien et al., 2000).

Despite the passage of the 1993 Revitalization Act, lack of enrollment of minorities and elderly persisted. Uncertain coverage by third party payers, including Medicare, was believed to be the primary reason for lack of participation. To address this problem, on June 7th, 2000, President Clinton announced that Medicare would begin to pay for the routine costs of care for beneficiaries enrolled in federally sponsored clinical trials (Iltis, 2005). This announcement further expanded the federal government's investment in cancer clinical trials. This commitment was reinforced with the Center for Medicare & Medicaid Service's (CMS) October 17th, 2007 announcement that it would continue coverage of clinical trials. In 2007, cancer represented the largest portion of NIH's investment equaling $4.754 billion or 16.6% of the budget (OMB, 2007). While great strides have been achieved in the enrollment of women and elderly in cancer clinical research, the lack of enrollment of minorities persists. Some researchers cite the federal government's role in the Tuskegee Syphilis experiments as a significant factor influencing Black patients trust of the medical establishment overall, especially with participation in clinical research (Shavers, Lynch, & Burmeister, 2002). However, other

researchers have demonstrated that racial differences are less significant when access to treatment is adjusted by socioeconomic factors (Gross et al., 2008).

A paradigm shift in the approach to cancer clinical trial research and drug development began to take place in the late 1990s with the approval of trastuzumab for patients with Her2+ breast cancer in 1998. This is generally recognized as the beginning of the era of personalized medicine in which academic researchers and drug companies began considering whether subgroups of patients may obtain more benefit from treatment than others. In 2001, gefitinib, an EGFR TKI, began to show anti tumor activity in advanced NSCLC. By 2003, gefitinib was approved by the FDA for advanced NSCLC and there were some indications that response rate varied based on patient ethnicity (Fukuoka et al., 2003). One of the significant limitations to research that took place from 2001 through about 2008 was that lung tumor tissue analysis was conducted retrospectively often after patients had already begun participating in the treatment clinical trial. In many cases, a second research study was conducted subsequent to the termination of the treatment clinical trial. Nearly all researchers recognized the limitations to this research approach. There was growing support for biomarker research to be conducted concurrent with the treatment trial or prospectively in the lab.

The epidemiologic approach of enrolling large cohorts of patients into treatment clinical trials fails to account for genomic variations in tumor tissue. The hope and promise of personalized medicine is that patients will be treated based upon the molecular profile of their specific tumor tissue. However, such an approach increases the

burden of accruing the right numbers of patients into the various arms of a clinical trial. Further, it places increased urgency on the need to recruit a diversity of patients.

Recently, the leaders of NIH and the Food and Drug Administration (FDA) discussed their vision to makes changes to their regulatory and funding structures to prioritize a personalized approach to medicine (Hamburg & Collins, 2010). As part of this approach, the NIH and the FDA will:

1) Invest in advancing translational and regulatory science
2) Define regulatory pathways for coordinated approval of codeveloped diagnostics and therapeutics
3) Develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and make information about tests readily available.

Hamburg and Collins (2010) also emphasized that for personalized medicine to succeed, it will require the FDA and NIH to expand their efforts to develop tissue banks containing specimens that will allow for broader assessment of the clinical importance of genetic variation across a range of conditions along with information linking them to clinical outcomes. They emphasized that this may require public–private partnerships to help move candidate compounds into commercial development.

Some researchers have cited the importance of companion diagnostics, which are packaged diagnostic kits such as the DxS kit described above. Companion diagnostics require FDA approval, as opposed to diagnostic assays like the one developed at

DF/HCC which need to be performed in laboratories approved by Clinical Laboratory Improvement Amendment (CLIA) for high complexity testing. DF/HCC is part of a group of leading AMCs that developed the Lung Cancer Mutation Consortium Protocol to conduct molecular analysis for a broad range of somatic mutations, some which are not yet clinically actionable, using multiplex mutational profiling system. As part of this protocol, all patients are screened for participation in tumor tissue analysis and it is an opt-out decision to not participate. This background is discussed in greater detail in chapter 2.

Definition of terms

In this paper, there are several specialized terms related to the process of obtaining and analyzing lung tumor tissue for diagnosis and treatment of lung cancer. Most of the definitions provided here were obtained from an NCI online resource: http://www.cancer.gov/dictionary.

Term	Definition
Bronchoscopy	An invasive procedure that uses a bronchoscope to examine the inside of the trachea, bronchi (air passages that lead to the lungs), and lungs. A bronchoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease. The bronchoscope is inserted through the nose or mouth. Bronchoscopy may be used to detect cancer or to perform some treatment procedures.

Term	Definition
EGFR assay	A laboratory test to detect a mutation in the epidermal growth factor receptor.
EGFR mutation	The genetic change in a lung tumor that has been identified as sensitive to a pharmacogenomic medication such as gefitinib (used outside the US) and erlotinib.
Endobronchial ultrasound-needle aspiration (EBUS-NA)	Invasive procedure to biopsy the mediastinal, hilar and interlobar lymph nodes. Endobronchial ultrasound enables very accurate localization of the extrabronchial structures, including vessels (using the power Doppler imaging) and lymph nodes. Using 10—40 mmlong needles makes a biopsy of nodes located in a relatively remote position from the bronchial wall possible (Szlubowski et al., 2010)(Szlubowski et al., 2009)
Endoscopic ultrasound-needle aspiration (EUS-NA)	A procedure which uses a thin, tube-like instrument that has a light and a lens for viewing, an ultrasound probe, and a biopsy needle at the end to obtain tumor tissue. It is inserted through the mouth into the esophagus. Also called EUS-FNA.
Epidermal growth factor receptor	The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called EGFR, ErbB1, and HER1.

Term	Definition
HER-2/neu intracellular domain protein	The cytoplasmic domain or intracellular domain (ICD) of the HER2/neu protein that exhibits tyrosine kinase activity. Based on sensitization theory, co-administration of trastuzumab (anti-HER-2/neu monoclonal antibody) and HER-2/neu intracellular domain protein may result in the potentiation of a HER2/neu-specific cytotoxic T lymphocyte (CTL) response against tumor cells overexpressing the HER2/neu protein. HER-2/neu protein, a glycoprotein cell surface receptor that is composed of an extracellular domain (ECD), a transmembrane domain, and an ICD, is overexpressed by many adenocarcinomas including breast adenocarcinoma.

Molecular diagnosis	The process of identifying a disease by studying molecules, such as proteins, DNA, and RNA, in a tissue or fluid.
Mediastinoscopy	A procedure in which a thin, tube-like instrument with a light, lens for viewing, and tool for removing tissues is inserted into the chest through an incision above the breastbone. It is used to examine the organs in the area between the lungs and nearby lymph nodes and to get tissue sample from the lymph nodes on the right side of the chest. It is considered the gold standard for staging the mediastinum.
Molecular marker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process. A molecular marker or biomarker may be used to evaluate body's response to a disease.
Personalized medicine	A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease
Pharmacogenomics	The process by which drug companies develop medications that target specific genetic changes in the tumor. In pharmacogenomic drug development, clinical trials often require the medical institution to analyze tumor tissue.

Somatic mutation	An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases.
Translational research	A term used to describe the process by which the results of research done in the laboratory are used to develop new ways to diagnose and treat disease.
Transbronchial needle aspiration (TBNA)	A minimally invasive bronchoscopic technique that provides a nonsurgical means to diagnose and stage lung cancer by sampling the mediastinal and hilar lymph nodes through insertions of needle during a bronchoscopy.
Transthoracic needle aspiration (TTNA)	An invasive procedure in which a needle is inserted under the guide of a CT scan through the skin into a lung lesion to diagnose and stage lung cancer.
Tyrosine kinase inhibitor	A substance being studied in the treatment of some types of cancer. Tyrosine kinase inhibitor BIBF 1120 blocks enzymes needed for cells to grow, and may prevent the growth of new blood vessels that tumors need to grow. It is a type of tyrosine kinase inhibitor and a type of antiangiogenesis agent. Also called BIBF 1120.

CHAPTER 2

As discussed in Chapter 1, four distinct bodies of literature informed the conceptual model that guided this research and hypotheses tested. This chapter provides a critical review of each of these bodies of literature.

Diffusion of innovation of healthcare services and technologies research

Diffusion of innovation is the process by which a new idea, knowledge, or technology is adopted, communicated through the social network, and either implemented broadly to the point of market saturation, or until diffusion fails and the innovation is shelved or taken off the market. Although one of the earliest studies of diffusion was conducted in the 1950s and analyzed prescriptions of tetracycline by physicians (Coleman, JS. Katz, E. Menzel, H., 1966), most of the subsequent research involves applications to business or consumer technology markets rather than healthcare services (Soleimani & Zenios, 2011). Over the past decade, there has been increased attention to the relationship between diffusion of innovation in healthcare and differences in access and outcomes of healthcare services. This attention was generated by the 2001 IOM publication, *Crossing the Quality Chasm: A New Health System for the 21st Century*, a title that is adapted from Geoffrey Moore's analysis of Roger's diffusion theory in the sentinel book *Crossing the Chasm* (Moore, 1991). Since its publication, this book has been considered required reading for business school students, particularly those who focus on entrepreneurship or marketing of products in the information

technology products. Like Roger's theory, it is a useful framework to consider. However, it lacks the complexities encountered when analyzing diffusion of healthcare services. The complexities of diffusion of innovation in healthcare services are discussed in a comprehensive review, commissioned by the National Health System in the United Kingdom (Greenhalgh, Robert, & Bate, 2008). One chapter in this publication discusses the fact that healthcare services are deeply rooted in an epidemiologic model of research and innovation. Such an approach relies heavily on rationalist and experimental approaches to evaluation of innovation with randomized clinical trials considered the gold standard (Greenhalgh et al., 2008). The epidemiologic approach takes a linear approach to the adoption of innovation. It presumes that once the evidence is established through RCTs, new scientific knowledge, which could include a change in clinical practice, new drug or device, among other innovations, would be implemented into practice (Greenhalgh et al., 2008). The limitation of an epidemiologic mindset to diffusion is discussed by researchers who have evaluated the delays, and in some cases complete failures, of translational research to be incorporated into patient care.

The term translational research has historically been used to describe the transfer of knowledge from basic sciences (bench) to produce new drugs, devices, and treatment options to improve patient care (bedside). It refers to the development and testing of new compounds, devices, treatment algorithms to establish an evidence base for regulatory approval, commercialization, and justification for reimbursement. Recognizing that historically many advances in basic sciences have been slow to become integrated into

improved clinical care, Dr. Zerhouni, the former Director of NIH, undertook an effort to reduce the silos that exist in academic medicine between laboratory and clinical scientists. In the seminal 2005 interview, Dr. Zerhouni described the funding of a new program entitled the Clinical and Translational Science Awards (CTSAs), a grant program to encourage academic medical institutions to improve collaboration between the lab and clinical research personnel (Zerhouni, 2005). Initially, academic clinical scientists were very excited about this initiative, hopeful that it would result in more rapid utilization of improvements in patient care. Just a few years later, in 2008, a commentary entitled, "The Meaning of Translational Research and Why It Matters," by Dr. Steven Woolf described the failures of a product driven approach of bench to bedside translational research, stating that the historical definitions of translational research are incomplete and a premature endpoint in the bench to bedside paradigm shift. Only half the patients in the US benefit from translational advances (McGlynn et al., 2003). Practice-oriented translational research, which is now being called T2 or TRIP (Translating Research to Practice), focuses on analyzing and overcoming barriers to the diffusion, dissemination, and adoption of clinical practice guidelines that incorporate T1 advances to the community.

In the case of the EGFR assay, T1 represents the period between 2004, linking the EGFR mutation to clinical responsiveness of the EGFR TKI, and the commercialization of the EGFR assay by Genzyme Genetics. T2 is the establishment of evidence based guidelines linking technological advances to improvements in patient care with

regulatory and reimbursement approvals. T3 is implementation of those guidelines and knowledge for reimbursement by the clinicians at the bedside and by the administrative and coding staff at the hospitals. T4 would be communicating information from successful diffusion back to researchers and those who conduct research that becomes the basis of clinical practice guidelines to inform prevention.

As has already been discussed in the review of the conceptual model, there are multiple levels of barriers to diffusion of innovation in healthcare services, including, but not limited to: 1) Complex and uncertain regulatory and reimbursement structure. 2) Role of principal/agent relationship in the physician referral to the innovation. 3) Delays in evidence being incorporated in clinical practice guidelines and lack of implementation of those guidelines at both an institutional and physician level.

The IOM recognized that some of these barriers were interfering with applications, developed as a result of sequencing the human genome, being incorporated into improvements in medical care, community and public health prevention, and treatment (Hernandez, Rapporteur, 2008). The IOM convened a workshop to discuss the issue and published a report of its findings. This report cited the work by Burke and colleagues (2006) who found that few promising genomic discoveries had resulted in actual applications in medicine. This report also included comments from Dr. Annetine Gelijns, who emphasized that the diffusion of genomic interventions is likely to be powerfully shaped by sociocultural factors, whereby even if genomic interventions are covered by insurers, patients may decide to pay out of pocket because of concerns about

confidentiality and the potential for discrimination by employers and insurance companies. This, in turn, raises concerns about equity—for example, about lack of access to these technologies for those who do not have the means to pay (Hernandez et al., 2008).

Also presenting at this workshop was Brad Gray, who was then vice president of product and business development at Genzyme Genetics. He described the specific problems that Genzyme Genetics had with diffusion of the EGFR assay.

> "There is a new paradigm for personalized medicine, however, one in which complex testing (some of which is genomic, some of which is proteomic, and some of which is other technologies) plays a central role in linking observation to tests and therapy. In such a paradigm, observation s followed by a test that provides specific information for better decision making. This, in turn, is followed by the action, which would be the therapeutic choice or regimen that leads to a predictable response, thereby breaking the cycle of trial and error"
>
> Referring directly to the experience Genzyme Genetics had with the EGFR assay, he wrote,
>
> "The company paid more than it had ever paid for an intellectual-property license and quickly drove a test to market. Soon afterward publications emerged that seemed to question the utility of EGFR mutation testing for driving dosing. Since that time there has been disagreement about which is the correct biomarker to predict response to this class of drugs. In July 2006 the C-Path Institute announced an effort to try to resolve the question of biomarkers in NSCLC cancer, but results are not yet available. When this product was taken to market, only a small minority of NSCLC patients who received TKIs—probably less than 5 percent—actually received the test, Gray said. The penetration is highest in the leading academic centers, where there is willingness and an ability to navigate the nuances of the emerging evidence. Community physicians, on the other hand, have generally been reluctant to adopt this approach. They are confused about the multiple-testing options, and they use what they consider clinical information (e.g., patient's race, smoking habits) as a proxy for the mutation status. Furthermore, because TKIs are most often used as the last line of treatment in these patients, there is a reluctance to do a test that would suggest that certain patients will not respond. The company learned several things from this

> experience. First, the connection between genetics and treatment is not always clear. Community physicians need education and assistance in understanding conflicting evidence. Robust clinical-utility data will be required to drive adoption by community physicians, who will continue to substitute work-around solutions when they are modestly effective. Furthermore, community physicians are not inclined, in general, to deselect patients from treatment. A test that selects patients in is much easier to sell than one that selects out, especially when there are few alternatives for those patients, Gray said. The adoption curve for EGFR testing is still heading upward. While the EGFR mutation test has not been adopted as rapidly as a new drug therapy typically would be, the indicators are moving in the right direction. The National Comprehensive Cancer Network (NCCN) guidelines for non-small-cell lung cancer include the test, a point which Genzyme Genetics believes will help community physicians gain comfort with the utility of the test. Based on past experience, then, Genzyme Genetics has revised its criteria for bringing new personalized medicine tests to market. First, for the company to invest in a test, the test needs to represent the only reliable way. Third, because reimbursement in the testing sector of the health care system has traditionally not been based on value but on activity-based costing, the economics must support investment in clinical and market development. The reimbursement path must be attractive, either by virtue of its intrinsic coding or because there is the possibility of making a compelling case to be reimbursed on a different basis than activity-based costs. Furthermore, the company will look for places to invest where intellectual property and know-how is available on an exclusive basis. In situations where only a non-exclusive product is offered, the company will not be able to justify the investment required to perform clinical research or to navigate the regulatory system. (Hernandez et al., 2008).

While Gray acknowledged the problem conflicting evidence poses for physicians when considering the adoption of new technologies, his analysis neglected to consider the role patients play in pulling an innovation through the market – even when there is conflicting evidence. It appears that Genzyme Genetics relied on a strategy of pushing the innovation through the market, viewing oncologists as their customers.

Although this is beyond the scope of this paper, an analysis of the breast cancer molecular diagnostic tests may illustrate an effort by the companies to market directly to breast cancer patients and survivors. Cancer patients, survivors, and caregivers can play a

powerful role in pulling innovations through the complex hurdles of regulatory and reimbursement barriers, getting physicians, who are slow to adapt to change, to adopt a new technologies.

When a diagnostic test is covered by Medicare and there are clinical practice guidelines that recommend its use, if a patient asks their oncologist or surgeon to order a test, it becomes much more difficult for that provider to decline the request. Gray's view of the problem will be discussed in much greater detail in Chapter 4.

Lung cancer clinical outcomes research

Lung cancer is the leading cause of cancer-related mortality for both women and men in the U.S. and worldwide. There are 1.35 million new cases and 1.2 million deaths yearly worldwide due to lung cancer (Parkin, Bray, Ferlay, & Pisani, 2005). In the US in 2010, there were 222,520 new cases of lung cancer and 157,300 people died as a result of lung cancer (Jemal, Siegel, Xu, & Ward, 2010). Lung cancer represents 14.5% of cancer incidence and 29% of cancer deaths in the US.

Platinum-based chemotherapy doublet is the standard care for most patients who present with late stage disease. This treatment offers patients modest improvements in survival (Schiller et al., 2002). However, in the past two decades, there have been significant advances in the understanding of lung tumor biology and molecular changes at the genetic level that contribute to oncogenesis. Although this understanding has not yet lead to significant increases in overall survival, for patients with specific genetic mutations or translocations, it has increased progression free survival. Continued

advances in the understanding of lung tumor oncogenesis will increase personalization and treatment of lung cancer with targeted drugs based on specific genetic abnormalities.

In 1981, it was discovered that the EGFR receptor was overexpressed in several cancers, including lung cancer (Kawamoto et al., 1983). By 1990, the class of drugs known as EGFR TKIs was discovered. In 2002, oncologists and researchers began publishing information about their growing knowledge of the molecular biology of lung tumors and the significant role of EGFR mutations in the development and progression of NSCLC. This same year, the first EGFR TKI, gefitinib, was approved in Japan. By 2004, international clinical trials of EGFR TKIs established a link between improvements in progression free survival and presence of an EGFR mutation in patients' lung tumors. Retrospective molecular tissue analysis of these clinical trials contributed to the development of the EGFR assay. Patients who had EGFR mutations had a higher response rate and longer progression-free survival when their treatment paradigm included erlotinib or gefitinib (Lynch et al., 2004; Paez et al., 2004; Shepherd et al., 2005). However, patients without EGFR mutations responded poorly to erlotinib and gefitinib (Mok et al., 2009). Mutations in the tumor suppressor gene (p53) and activation of the Kirsten-Rous sarcoma virus (K-ras) oncogene were associated with poorer prognosis (Eberhard et al., 2005; W. Pao & Miller, 2005; Tol et al., 2009). KRAS incidence rate is thought to be between 20-30% in NSCLC patients and there are currently no targeted treatment options for KRAS mutations.

Although previous studies provided evidence that incidence of EGFR mutations varies with patient ethnicity, gender, and smoking status (Fukuoka et al., 2003; Jackman et al., 2007; W. Pao & Miller, 2005), more recent studies indicate that clinical characteristics are limited predictors of mutational status. If only women who were never smokers were tested for EGFR mutations, 57% of all EGFR mutations would be missed (D'Angelo et al., 2011). EGFR mutations have often been reported to be approximately 15% in Whites, 2-3% in Blacks, and 20-30% in Asians living in the US (Calvo & Baselga, 2006; Leidner et al., 2009; Mok et al., 2009; Yang et al., 2005). However, the recent evidence weakening the relationship between smoking status and incidence of mutation, underscores the importance of including a large and diverse patient population in biomarker clinical trials. Clinical practice should not be based on incomplete or inaccurate anecdotal assumptions developed by a limited patient population enrolled in clinical trials. It also emphasizes the importance of providing access to lung tumor genotyping for all patients with adenocarcinoma of the lung.

More recently, there was a discovery that patients with a translocation in the echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase (EML4-ALK) have a 52% response rate to an ALK inhibitor crizotinib (Kwak et al., 2010). According to Ding et al. (2008) and Pao & Girard (2011), as of January 2010, the following mutations were known in NSCLC: HER2, PIK3CA, MET, BRAF, MAP2KI, and AKT1, which are thought to have a less than 5% incidence rate each, ALK and

EGFR which are thought to have between 5-15% incidence rate each, KRAS and yet to be discovered mutations have a 30% rate each.

Even with these promising advances, the prognosis for patients with lung cancer is dismal, complicated by the fact that the disease is most often diagnosed in late stages when the cancer has spread beyond the lungs. This is illustrated by the fact that over 60% of lung cancer patients are diagnosed with advanced disease at stage III or stage IV (Ries et al, 2008).

While there have been improvements in the rate of short-term survival, according to the NCI Surveillance, Epidemiology, and End Results (SEER) Program (2008), these have not been translated into significant improvements in long-term survival. In 1975, 36.7% of patients survived 1 year. By 2004, this rate improved to 43.3%. The five and ten year survival rates have not seen significant improvements. In 1975, 13% of patient survived 5 years. By 2004, this rate only improved by 3.2% to 16.2% of lung cancer patients living to 5 years. When this analysis is extended to 10 year survival, there has only been a .8% improvement with 9.2% of patients in 1975 surviving 10 years and 10% of patients in 2004 surviving ten years.

The five-year survival rate for patients diagnosed with lung cancer is even worse worldwide. It is 15% for those living in the US, 10% in Europe and 8% in the developing world (Parkin et al., 2005). Beyond differences in outcomes worldwide, several studies have documented differences in incidences rates, treatment, and outcomes in the US between minorities and Whites.

Lung cancer disparities research

For more than two decades healthcare providers and policy makers have known about racial disparities in the treatment and outcomes of lung cancer. There is an established body of research that has demonstrated differences in access to chemotherapy, radiation, and surgical treatment of lung cancer (Gross, Smith, Wolf, & Anderson, 2008; Herrin, Wong, & Krumholz, 2005; Lathan, Neville, & Earle, 2006; Bach, Cramer, Warren, & Begg, 1999). Other studies have found that higher levels of co morbidity, later stage diagnosis and poorer performance status among Black lung cancer patients contribute to poorer outcomes (Blackstock et al., 2006). These differences contribute to higher rates of morbidity and mortality for minority lung cancer patients.

Prior to age 45, Blacks have a significantly lower risk of being diagnosed with lung cancer than White men (Karami, Young, & Henson, 2007). However, after age 45, differences in incidence, mortality, and survival rates between Black men and White men are dismal. Although there are significant differences in mortality rates between White and Black men, the lifetime risk for Black men to be diagnosed with and die from lung cancer is similar to White men. This is because Black men have other significant health burdens as they reach middle age, which causes earlier mortality. The lifetime risk of diagnosis for lung cancer is 7.86 for White men and 7.75 for Black men. The lifetime risk of death due to lung cancer is 7.17 in White men and 6.99 in Black men. The median age at diagnosis of lung cancer in Black men is 66 years old, five years earlier than whites. Black men experience a significantly higher rate of age adjusted incidence of lung

cancer compared to White men. 28.3 more Black men per 100,000 are diagnosed with lung cancer than White men. A similar difference exists in the age adjusted death rate. 21.8 more Black men per 100,000 die from lung cancer than White men. It is worth noting that, although a similar disparity exists between Black and White women, it is far smaller at 2.1 more deaths per 100,000 Black women than White women. The most significant racial disparity in lung cancer is in the incidence, death, and five year survival rates per 100,000 patients. The incidence rate in Black men is 28.3 per 100,000 higher than in White men. The death rate is 21.8 per 100,000 higher. And, the five year survival rate is 3 patients per 100,000 lower (Jemal A, Siegel R, Ward E, et al, 2008).

Table 5 summarizes the racial disparities in outcomes for lung cancer patients. These statistics clearly illustrate that Blacks, men in particular, bear a disproportionate share of the lung cancer burden.

Table 5

Racial Differences by Gender on Measures of Lung Cancer Morbidity and Mortality

Measure	Total Both Sexes	Total Males	Total Females	Whites Both Sexes	Whites Males	Whites Females	Blacks Both Sexes	Blacks Males	Blacks Females
Estimated new cases of lung cancer in 2008	215,020	114,690	100,330						
Estimated new deaths from lung cancer in 2008	161,840	90,810	71,030						
Prevalence	360,081	172,426	187,655						
Person life years lost	2437.767								
5 Year Survival per 100,000	15.2	13.1	17.6	15.5	**13.4**	17.9	12.1	**10.4**	14.5
Incidence per 100,000 age adjusted	63.9	79.4	52.6	65.1	**79.3**	54.9	76	**107.6**	54.6
Deaths per 100,000 age adjusted	54.1	72	41	54.4	**71.3**	42	60.9	**93.1**	39.9
Lifetime risk for diagnosis of lung cancer	6.94	7.78	6.22	7.13	**7.86**	6.52	6.54	**7.75**	5.45
LIfetime risk of dying from lung cancer	5.98	7.08	5.02	6.12	**7.17**	5.21	5.49	**6.99**	4.18
Trends (annual % change) in mortality	-1	-2	0.1	-0.9	**-1.8**	0.2	-1.7	**-2.8**	0.1
Trends (annual % change) in incidence	-1.4	-2.2	-0.5	-1.3	**-2.1**	-0.6	-1.7	**-3.2**	0.4

Based on SEER data from 1995-2004

Notes: Incidence projections are based on rates from the North American Association of Central Cancer Registries(NAACCR) from 1995-2004, representing about 85% of the US population.

SEER 17 areas (San Francisco, CT, Detroit, HI, IO, NM, Seattle, UT, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native US Mortality Files, National Center for Health Statistics, CDC.

SEER 17 areas. California excluding SF/SJM/LA, Kentucky, Louisiana, and New Jersey contribute cases for diagnosis years 2000-2004. The remaining 13 SEER Areas contribute cases for the entire period 1996-2004.

Table 6

White/Black difference in each measure

Measure	Male	Female
5 Year Survival per 100,000	3	3.4
Incidence per 100,000 age adjusted	-28.3	0.3
Deaths per 100,000 age adjusted	-21.8	2.1
Lifetime risk for diagnosis of lung cancer	0.11	1.07
LIfetime risk of dying from lung cancer	0.18	1.03
Trends (annual % change) in mortality	1	0.1
Trends (annual % change) in incidence	1.1	-1

Notes: Calculated from table 5 by subtracting Black from Whites.

Source: Author's construction from SEER data from 1995-2004

The lack of minority enrollment in lung cancer clinical trials and under representation of minorities at NCI cancer centers may contribute to some of the existing disparities in lung cancer outcomes. Lack of representation in lung cancer clinical trials may also be

contributing to limited information about the actual incidence and significance of racial differences in lung tumor molecular biology. Given the growing approach to personalized cancer care, in which the knowledge of tumor biology informs drug development research, under representation of patients from specific ethnicities or race in biomarker clinical trials research may be widening the gap in cancer outcomes.

The reasons for differences in enrollment of ethnic and racial minorities are mutlifactorial. Several studies illustrate the relationship between likelihood to enroll in clinical research and age, race, socioeconomic status, rural/suburban residence, proximity to comprehensive cancer centers, availability of transportation, comorbid conditions, type of cancer diagnosis, and religious/spiritual beliefs (Adams-Campbell et al., 2004, Advani, Goldstein, & Musen, 2002, Murthy, Krumholz, & Gross, 2004).

More recent medical research illustrates that healthcare provider and market factors also influence enrollment in clinical research (Gross & Krumholz, 2005). Implications for lower minority enrollment in lung cancer clinical trials are best illustrated by an analysis of the knowledge about incidence of EGFR mutations in blacks.

Clinical trials of EGFR mutations and EGFR TKIs

The incidence rate of EGFR mutations in Blacks is derived from two studies (Leidner et al., 2009; Yang et al., 2005). These studies analyzed a total of 94 patients who self identified as Black. Both studies sought to confirm information that has generally become believed by thoracic oncologists, despite limited published evidence with small sample sizes, that EGFR mutation in Blacks is rare. Most Black patients that participated

in Yang's study were from the University of Maryland Medical Center. One Black patient was from Mayo Clinic in Minnesota. All patients that participated in the trial by Leidner et al. (2009) were from University Hospitals Case Medical Center in Cleveland, Ohio. The incidence rate of EGFR mutations in the Yang study was 2.4% or 1 patient. Similarly, Leidner and colleagues reported 1 patient (2%) among their 53 Black patients tested positive for EGFR mutations.

The limited published evidence about the incidence of EGFR mutations in Blacks prompted the author to conduct a systematic review to determine whether sufficient numbers of Black patients were included in these studies to establish evidence on incidence rate of EGFR mutations in Blacks. This review analyzed thirty six multi institutional domestic and international EGFR TKI clinical trials and retrospective molecular tissue studies which took place between 2001and 2010.

Table 7 lists the studies analyzed

Table 7

Name of Clinical Trial, Compound, and Number of Patients

Trial Name	Year Reported	Number of Patients	Compound
IDEAL-1	2003	210	Gefitinib
IDEAL-2	2003	221	Gefitinib
INTACT-1	2004	1093	Gefitinib
INTACT-2	2004	1037	Gefitinib
BR.21	2005	731	Erlotinib
SO126	2005	135	Gefitinib
TRIBUTE	2005	1059	Erlotinib
ISEL	2005	1692	Gefitinib
iTarget	2008	98	Gefitinib
INVITE	2008	196	Gefitinib
SO341	2008	81	Erlotinib
SWOG S0023	2008	571	Gefitinib
INTEREST	2008	1466	Gefitinib
SATURN	2010	889	Erlotinib

Notes: Summarizes patients that participated in U.S. multisite EGFR TKI clinical trials
Source: Author's construction from systematic review of EGFR TKI clinical trials

This review revealed that Blacks represented less than 3% and Hispanics represented less than 1% of patients of phase II and III studies. These results are demonstrated below.

Table 8

Number of Studies Reporting Ethnicity/Race by Phase of Research

Type of Study	# of Studies	Race/ Ethnicity not reported	Reported only Whites & Asians	Reported Blacks
Phase I	4	4	0	0
Phase II	12	3	5	4
Phase III	9	0	2	7
Molecular	12	3	6	3
Total/%	37	27%	35%	38%

* Several molecular studies were conducted on phase I and II trials already presented in table.

Notes: Studies included in systematic review categorized by stage
Source: Author's construction

Table 9

Ethnicity and Race Reported of Patients in Phase II and III Studies

Reported Race/Ethnicity in Phase II & III studies of EGFR/TKIs

	Phase II	Phase III	Total	%
White	811	6679	7490	76%
Black	14	233	247	3%
Asian	2	1002	1004	10%
Hispanic	154	65	219	2%
AI/AN	0	4	4	0%
Other	98	804	902	9%
Total	1079	8788	9867	100%

Notes: Studies included in systematic review categorized by stage, ethnicity and race reported
Source: Author's construction

Many studies analyzed were conducted after the 2003, 2004, and 2005 regulatory approval and commercialization of EGFR TKIs and the EGFR assay. Yet, this systematic review of EGFR TKI studies clearly indicated barriers exist in access to these important advances in diagnosis and treatment among minority populations. No studies to date have analyzed whether institutional and regional differences in the diffusion of lung tumor genotyping technologies contributes to a lack of access and hence a lack of understanding about lung tumor biology in minority populations. This background and summary clearly demonstrate the urgency of understanding barriers to the diffusion and utilization of molecular diagnostic technologies for minority populations. These technologies have become an important tool in the discovery of genetic alterations that lead to carcinogenic pathways in lung cancer. These studies are also a tool in the development of new treatments.

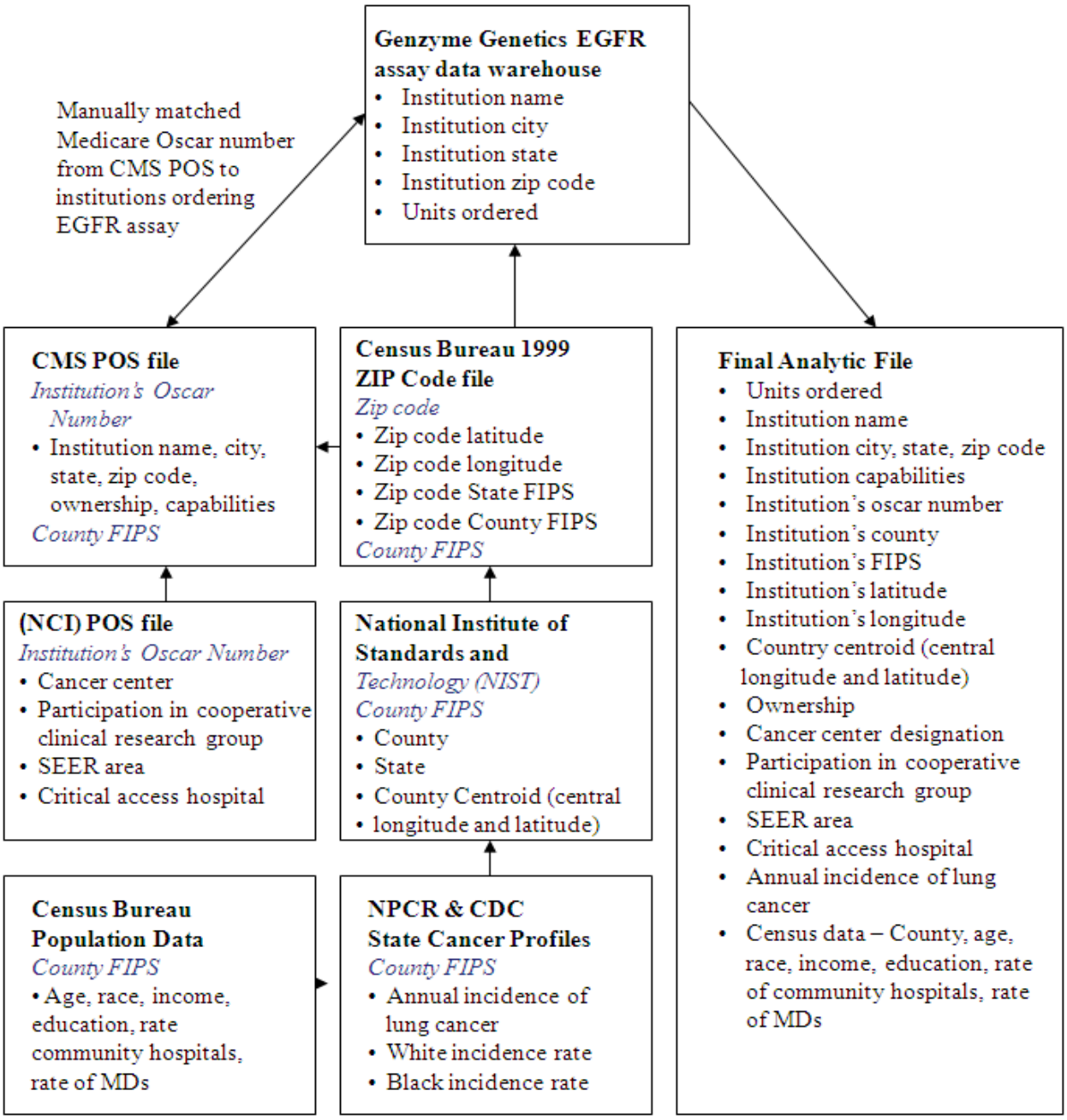
CHAPTER 3

Methods

This is a cross sectional, retrospective, observational study, which uses secondary data analysis research methods to analyze seven datasets which were merged into two separate analytic files. One analytic file has institutions as the unit of analysis. The other analytic file has county as the unit of analysis. Of the datasets merged, one was proprietary. It contained the key dependent variable, number of orders placed for the EGFR assay from Genzyme Genetics for the calendar year 2010. The independent variables analyzed were obtained from seven publically available datasets which were merged with the EGFR data warehouse to create two analytic files. The unit of observation in the principal analytic file was acute care hospitals and institutions in the US that ordered the EGFR assay. The unit of observation in the second analytic file, a contracted version of the first, was counties in the US in which acute care hospitals are located. The study involved less than minimal risk to human subjects because it used existing administrative billing data that was de-identified. A description and source for the public datasets is listed in Table 11. A flowchart illustrating the process for joining these datasets is provided below.

Figure 5

Flowchart of Process for Linking Datasets to Create Analytic File



Description of proprietary dataset

On April 15, 2011, Genzyme Genetics, the company which owned the rights to distribute the EGFR assay, extracted all the orders for the EGFR assay in US territories for the calendar year 2010 from their data warehouse. This dataset was emailed to the researcher on April 22, 2011. It included variables about the name, city, state, zip code, and number of units sold to each hospital or lab requesting EGFR analysis. It also included the gender and payer of the patient. According to Genzyme Genetics, this data set represents approximately 98% of the EGFR assays conducted on behalf of community hospitals within the United States. However, this dataset is not a comprehensive representation of EGFR assays conducted at NCI CCs.

NCI CCs, particularly those that are characterized as comprehensive centers, often have their own CLIA certified labs and the capability to conduct EGFR assay alone or as part of a multiplex of mutations sequenced independent of Genzyme Genetics. The researcher contacted a few NCI CCs to corroborate this information. Although the EGFR assay warehouse does not represent a comprehensive picture of NCI CC utilization, there is some information about the NCI CCs. For example, Moffit Cancer Center in Tampa, Florida and Mayo Cancer Center in Rochester, Minnesota have contracts with Genzyme Genetics to conduct EGFR analysis at a special contracted rate. Therefore, information about these two centers is likely complete. Additionally, there were a large number of tests ordered from Johns Hopkins and Duke University, which suggest that these institutions are also sending all their requests for an EGFR assay to Genzyme Genetics,

rather than processing these within its own lab. Table 10 summarizes the original data Genzyme Genetics provided characterized by type of institution.

Table 10

Number and type of institutions ordering EGFR assay

Type of Institution	Number	Assays Ordered	Percent of total
Acute care hospitals	592	6058	76.2
Federal hospitals (Veterans Administratio	15	93	1.2
NCI CCCs	27	1019	12.8
Pathology labs	60	527	6.6
Independent outpatient oncology clinics o	48	258	3.2
	742	7955	1

Source: Genzyme Genetics EGFR assay data warehouse

In the original data file that Genzyme Genetics sent, there were 7,957 units of EGFR assay ordered as part of 7,804 orders. Orders from institutions that resided outside the continental US were removed from the data set leaving 7955 tests ordered from 742 different institutions. In total, there were 1019 tests ordered from 27 NCI CCs. For the purpose of consistency, all tests ordered from NCI CCs were removed from the dataset so that this information was not included in the analysis.

Description of public datasets

The variables included in the public data sets are represented either at the institutional level (CMS/NCI provider of service file) or at the county level. Each of these datasets and the variables of interest are described in Table 11. There are 3,142 counties, county equivalents, or independent cities in the US. Each county is assigned a state and

county level FIPS code. Combined these make a unique identifier for each county.

Table 11

Public Use Data Sets

Source	Description
Census Bureau Population Data	This dataset was downloaded from the website: http://www.census.gov/population/www/popdata.html. It contains county level population characteristics (size, ethnicity/race, income, education, number of hospital beds, physicians, and community hospitals).
Census Bureau 1999 ZIP Code file	This dataset was downloaded from the website: http://www.census.gov/geo/www/tiger/zip1999.html. It contains a list of the United States' zip codes, latitude, longitude, city, county and state federal information processing standards codes (FIPS). FIPS codes uniquely identify geographic areas. State-level FIPS codes have two digits, county-level FIPS codes have three digits and are unique within each state.
National Institute of Standards and Technology (NIST)	This dataset was obtained from the following website: http://www.itl.nist.gov/fipspubs/co-codes/states.txt. It provides a list of county and state level FIPS codes.

The National Program of Cancer Registries (NPCR) and Centers for Disease Control and Prevention (CDC) State Cancer Profiles	This dataset was obtained from the website: http://statecancerprofiles.cancer.gov/incidencerates/index.php. It provides state and county level lung cancer incidence through 2008.
2009 Center for Medicare and Medicaid Services (CMS) Provider of Services (POS) file	This dataset was obtained from CMS. Institutions that bill CMS for patients are required to submit an annual survey that provides information about the institution's ownership and operational characteristics. Each institution that provides Medicare patients with healthcare services is assigned a unique identifying number called the Oscar number.
2010 National Cancer Institute (NCI) POS file	NCI enhanced the CMS POS file with information about institutional participating as a designated cancer center or in NCI sponsored cooperative. The researcher paid a fee of $150, the cost to develop an unencrypted version of the file that revealed the institution's Medicare Oscar number so that the researcher could link the NCI variables with the CMS POS file directly.

U.S. Department of Agriculture division of Economic Research Services (USDA ERS)	This dataset was downloaded from the website: http://www.ers.usda.gov/Data/TypologyCodes/. It's a 12 code classification system based on county rural/urban and metropolitan status. 1 and 2 are assigned to small and large metropolitan areas based on population of 1million residents.

Creating the analytical file

All patient identifiers were removed from the dataset Genzyme Genetics provided. However, the name, address, and zip code of each institution that ordered the EGFR assay on behalf of patients were provided. The researcher aggregated these individual patient orders to the institutional level then obtained the institution's Oscar identification number from the CMS POS file. The Census Bureau zip code file was merged with the EGFR data warehouse to assign a FIPS number to each institution. Once the acute care hospitals in the EGFR dataset were assigned the correct Oscar number, the NCI POS file and CMS POS files were merged with the EGFR assay data warehouse. Then, using the FIPS number of each institution, the publicly available data sets from the Census, National Program of Cancer Registries and the Centers for Disease Control (CDC) were merged with the EGFR data warehouse, to create the final analytic file.

Refining the Public Data Sets

Datasets needed to be sorted and condensed.

Table 12 summarizes those changes.

Table 12

Summary of Changes Made to Original Data Files

Datasets with county characteristics	
Counties in the US	3,142
Counties without acute care hospitals removed from analytic file	646
Counties in analytic file	2,496
Datasets with institutional characteristics	
Hospitals in original CMS/NCI files	11,656
Hospitals removed: Psychiatric, Christian Science, and long term care facilities; Outside continental US, duplicates due to change of status (CAH filing, change of ownership, other), closed facilities.	6,983
Institution added: Independent pathology labs, cancer centers, physician offices from Genzyme Genetics dataset with no Oscar Provider Number	107
Institutions in the analytic file	4,780
Institutions by type of service provider	
Acute care hospitals	3020
Independently operated pathology labs	60
Independent physician offices or outpatient cancer centers	47
Veterans Administration Hospitals	159
Military hospitals	154
Prisons	22
US Public Health Service	22
Critical Access Hospitals	1296
Institutions in the regional analytic file	5244
Final number of institutional observations from Genzyme data	745
Counties ordering EGFR assay	383

Notes: Four counties had utilization rates exceeding 1, which is likely due to testing on patients that were diagnosed in previous years, or patients from other counties seeking care within these counties. Counties and the number of tests ordered included: Miami-Dade, FL (78); Winchester, VA (30); Montour, PA (31); Andrew, MO (54). In total, 193 orders from 42 institutions were removed as outliers.

Source: Author's construction from CMS Provider of Service file and Genzyme Genetics EGFR assay data warehouse

Counties without acute care hospitals were removed from the final county analytic files. Hospitals that were unlikely to be treating lung cancer patients were removed. These included psychiatric, Christian Science and long term care facilities. Analysis was limited to diffusion of the EGFR assay within continental US. Therefore institutions operating outside the US were removed.

The most time consuming process of refining the data was culling out duplicates or inactive hospitals from the CMS/NCI POS files. Most research that analyzes the relationship between quality of care and institutional characteristics licenses the American Hospital Association (AHA) database for approximately $5000. The cost to license this was beyond the resources available to the researcher. Therefore it required significant investment of time identifying and deleting dated, duplicated, or closed facilities that continue to have an active provider (Oscar) numbers in the CMS database. It should also be noted that the AHA database does not include the required variables from the NCI. Although NCI dataset is public, most researchers use it through SEER and the institution's identification is encrypted.

Effort was invested in matching the name and address of the institution as listed in the Genzyme Genetics Warehouse to their names in the CMS/NCI POS file. In some cases it was exactly the same name. In other cases one dataset used the university name while the other used the hospital name. There were no cases where the matching was not apparent. However, in several observations, independent pathology laboratories were operating within, or on behalf of, an acute care hospital. When this relationship could be

conclusively established, the order was assigned to that acute care hospital. However, there were 108 institutions (60 pathology labs and 47 physician offices or outpatient cancer centers) that were included in the analytic file but whose affiliation could not be directly linked to an acute care hospital. These observations had institutional characteristics listed as missing and will be dropped from any regressions that use institutional capabilities, or participation in NCI cooperative group variables. A similar dynamic existed with the institutions owned by the Federal government. Federal institutions are exempt from filing the requisite updates to the CMS POS file. Yet, some of the Veterans Health Administration hospitals (VA) participate in NCI cooperative groups and see Medicare patients. Therefore, in some VA observations, the institutional characteristics are listed whereas in other observations these are missing. The researcher could identify no timely and accurate way to impute the missing data. Therefore, for those observations that are missing institutional characteristics, the observations will be dropped from any regressions that use these variables. However, these observations are included in the regional analysis. These limitations in the dataset will be discussed in the results and conclusions.

In the CDC/NPCR datasets, data on annual number of lung cancer cases and lung cancer incidence are based on the year 2008. These data were submitted via the states cancer registries to the CDC/NPCR in January 2010 and made available to the public and researchers in August 2011. These data was for the most part comprehensive and

complete. However, there were some counties in which data was suppressed. The basis for imputing data for these counties is discussed below.

For all counties in the states of Kansas and Minnesota, state policy prohibits releasing data outside the county. For counties in Kansas and Minnesota, the average annual lung cancer cases and incidence for male and female from years 2002 – 2006 were provided on state web sites. From these numbers, total annual number of cases and incidence per county were imputed using the same age and population adjustment methodology SEER uses.

In 221 counties that had fewer than 3 lung cancer cases per year, data was suppressed due to confidentiality. For these counties the number 1 was imputed. For these same counties, if the average annual incidence was below 16, these numbers were suppressed due to confidentiality. In these 221 counties, I assumed the lung cancer cases on average were 8. For 62 counties and parishes in Alabama, Mississippi, Louisiana, and Texas, data was suppressed due to population shifts that resulted after hurricane Katrina. The average annual number of cases in these counties was imputed from the year prior to hurricane Katrina.

Once the final analytic file was created, several additional derivative variables were calculated and generated. The county age, education, and income data was originally included as a continuous variable, percent of the county population. However, when incorporating these variables into stage 1 and stage 2 logistic regression models, the collinearity between these variables caused the model to fail. Transforming these

variables to a dichotomous variable based on the mean, allowed the model to run. The solution to this was to change it to a when that data These include:

Table 13
Variables generated from original datasets

Variables created for analysis of NCI CC in county		Coded
NCI	Institution is an NCI CC	0/1
Ed_BS_Mean	County has above the mean (17%) of residents with BS degree	0/1
Ed_BS_45%	County has more than 45% of residents with BS degree	0/1
Income_75K_Mean	County has above the mean (14%) of residents with Income greater than $75, 000	0/1
Age_under_45_Mean	County has above the mean (59%) of residents with Income greater than $75, 000	0/1

Variables created for institutional analysis - institutional characteristics and likelihood of ordering EGFR assay		Coded
Chemo, Pet, Cardiothoracic surgery, Med school	All variables about institutional capability, were originally coded as 0 - 4. 0 - no capability; 1,2,3 provided by staff, agreement, or combination recoded as 1	0/1
Coop	Institution participated in any NCI clinical research group	0/1
NonCoop	Non Coop	0/1
Recipient	Non NCI CC	0/1
Distance_NCI	Calculated as miles between Recipient hospitals (Non NCI CCs) and NCI CCs	0-1921
Closest_NCI	NCI CC for which the Distance_NCI is calculated	Name of hospital
Num_EGFR	Number of EGFR assays institution ordered	0-168
Inst_EGFR	Whether institution ordered even 1 EGFR assay	0/1
EGFR_rate	Number of EGFR assays ordered in county/annual lung cancer cases	0-.9

Variables created for regional analysis of EGFR rate and county characteristics		Coded
Ids_in_FIPS	Hospitals in county	
Med_in_FIPS	Hospitals with a medical school affiliation in county	0-36
Coop_in_FIPS	Hospitals that participate in NCI clinical research group in county	0-24
Chemo, MRI, Pet, Cardiothoracic surgery_in_FIPS	Hospitals with a Chemo, MRI, Pet Scan, Surgery capabilities in county	0-24
NCI_in_FIPS	NCI CC in county	0/1
EGFR_FIPS	Number of EGFR assays ordered in county	0-249
EGFR_Inst_FIPS	Number of institutions ordering EGFR assay in county	0-16

Statistical Methods

Descriptive statistics will be used to summarize the variables within the three equations of the conceptual model. Univariate analysis will be used to summarize the categories of institutions ordering the EGFR assay and the characteristics of the hospitals and counties. Bivariate analysis will be used to summarize the location of the NCI CCs, institutional and county characteristics by status of ordering the EGFR assay.

Generalized linear models will be used for testing hypotheses. Logistic regression will be used to test equations 1 and 2 of the model, which is the likelihood a county has an AMC that obtains NCI designation and the likelihood an institution orders an EGFR assay. Multivariate regression will be used to test the contribution each independent variable makes toward predicting the dependent variables of equation 3, EGFR rate. Logistic and multiple regression will determine whether the independent variables are having the hypothesized effect based upon whether the odds ratios are different than 1 or

the coefficients are greater than 0. Both the logistic and multivariate regressions will be conducted by manually stepping in each independent variable to analyze the correlation between the independent variables and the subsequent impact on the odds ratios or coefficients.

Methodological challenges

There were several challenges working with these datasets. A major drawback to this dataset is that it lacks patient level data. As has been demonstrated in Chapters 2 and 3, the driving motivation behind this study was to determine whether racial disparities in access to the EGFR assay contribute to lack of knowledge about the incidence of EGFR mutations in Blacks. It was hoped that regional analysis of diffusion might explain the hypothesized racial difference in access to the EGFR assay. Yet, for two reasons, regional analysis failed to establish a racial disparity in access to the EGFR assay. The fact that NCI CCs locate in metropolitan counties which have dense Black populations suggests that there are not regional barriers to access for the EGFR assay. However, regional analysis fails to consider the age of the minority populations in communities close to the NCI CC. Minority populations living close to NCI CCs tend to be younger than the population of patients who get cancer, therefore they may not be seeking care at the NCI CCs. Further, there are a large percentage of whites living in rural, non metro counties that are not being provided access to the EGFR assay. Therefore, even when the patient level data is analyzed, the hypothesized racial disparity may not be significant given the equivalent disparities among White populations. Without the patient level data from the

Medicare claims files, it is not possible to prove that Black patients are not accessing the assays that the NCI CCs are conducting. Therefore, this dataset does not allow that question of racial disparities to be analyzed.

The lack of comprehensive data on NCI CC testing is also a drawback in the dataset. Table 3 suggests that the number of EGFR assays conducted by NCI CCs may exceed the number of assays conducted nationally. The absence of this data from the analysis weakens the explanatory power of any model to determine regional causes that drive the EGFR diffusion rate (equation 3). If this data were included, there would likely be very high utilization rates in counties which have an NCI CC, or those in close proximity to these counties, with low or zero utilization in distant counties.

There are several other factors that may both strengthen and weaken the explanatory effect of the model. 503 counties in the US have no acute care hospitals located within their boundaries. These counties were removed from the dataset on the premise that patients would not have access to the required medical procedure to obtain tumor tissue. However, some of these patients are likely traveling to other counties to obtain care. It is difficult to capture the impact border crossing has on the regional EGFR rate without having access to the patient data. The challenge that border crossing poses to regional analysis of healthcare utilization applies even when there is are acute care facilities located within the counties. Cancer patients may be more likely to travel to seek care in specialty hospitals. This may have been one of the factors contributing to 4 counties within the US having utilization rates above the number of annual lung cases for

that county. If this happened with other counties, this may be giving greater weight to the sociodemographic variables of the counties in which patients are seeking care and weaken the effect of the distance to NCI CC variable.

Logistic regression tends to systematically overestimate odds ratios or beta coefficients when the sample size is less than about 500 (Nemes et. al, 2009). Although the sample size of both the institutions and counties is greater than 500, the outcome of counties ordering the EGFR assay is only 379 of the 2,359 counties analyzed. Similarly, once NCI CCs and outliers were removed from the dataset, there were only 708 institutions of the 7007 institutions analyzed. This may result in an overestimation of the odds ratios and beta coefficients. Therefore, sensitivity testing will be conducted on the model and it will be run in several different ways, eliminating counties that have no acute care facilities from the analysis as well as running the regression only on those counties which have at least 1 institution that has ordered an EGFR assay.

These methodological problems underscore the importance of conducting an analysis of patient access to lung tumor genotyping using the Medicare claims data on individual patients. The vast majority of lung cancer patients are Medicare patients. Therefore, analysis of the 331,000 lung cancer patients Medicare claims file will provide a comprehensive analysis of quality of lung cancer care and variable driving access to personalized cancer care.

CHAPTER 4

Equation 1 Results

The first step in the conceptual model was to determine the likelihood a county has a hospital that obtained NCI designation.

Table 14 is an analysis of the county typology, as defined the US Department of Agriculture Economic Research Services (USDA ERS), with the location of NCI CCs, acute care and critical access hospitals, institutions ordering the EGFR assay, number of assays ordered, percentage of the US population, percentage that is black, and lung cancer incidence.

Sixty of the sixty two NCI CCs are located within large or small metropolitan counties which also have a higher percentage of residents that self identify as Black. However, to test this when considering the other independent variables, a logistic regression is required.

Table 14

Descriptive analysis of geographic location of NCI CCs, hospitals, and EGFR assay orders

2003 Code	Description	Ctys	NCI CCs	Hosp.	CAH	Hospitals ordering assay	EGFR assays ordered	% of US Pop	% Black	Ann Inc LC
Metropolitan counties:										
1	Large metro - 1+ million residents	413	44	2440	61	436 (.59)	4274 (.62)	.53	.17	66.41
2	Small metro - Less than 1 million residents	676	16	1753	169	226 (.30)	2171 (.31)	.30	.11	70.24
Nonmetropolitan counties:										
3	Micropolitan - adjacent to large metro	92	1	149	30	9 (.01)	25 (.00)	.02	.07	77.12
4	Noncore adjacent to large metro area	123		80	65	1 (.00)	6 (.00)	.01	.09	76.19
5	Micropolitan area adjacent to small metro area	301		423	97	40 (.05)	269 (.04)	.05	.09	73.53
6	Noncore adjacent to small metro Contains a town of at least 2,500 residents	358		497	244	9 (.01)	75 (.01)	.03	.10	72.14
7	Noncore adjacent to small metro area and no town of at least 2,500 residents	185		43	99	0 (.00)	0 (.00)	.01	.08	65.29
8	Micropolitan area not adjacent to a metro area	282	1	322	93	18 (.02)	72 (.01)	.03	.08	70.16
9	Noncore adjacent to micro area Contains a town of at least 2,500 residents	201		103	147	1 (.00)	1 (.00)	.01	.08	71.16
10	Noncore adjacent to micro area No town of at least 2,500 residents	198		47	99	0 (.00)	0 (.00)	.00	.07	58.18
11	Noncore not adjacent to metro or micro area. Contains town of at least 2,500 residents	138		92	94	3 (.00)	3 (.00)	.01	.04	64.08
12	Noncore not adjacent to metro or micro area. No town of at least 2,500 residents	174		46	100	2 (.00)	3 (.00)	.00	.02	54.10

Notes: Ctys is counties; Hosp. is hospitals; CAH is critical access hospital; Ann Inc. LC is annual incidences of lung cancer per 100,000 people.
Source: Author's construction.

Table 15 illustrates the results of the logistic regression analyzing the likelihood a county has a hospital which obtained NCI designation. It illustrates the progressive effect each independent variable added to the model has on the odds ratios of the other variables. The chi-square of .0000 indicates that there is essentially no possibility of the null hypothesis that the independent variables proposed, operating together, are unrelated to the dependent variable, location of hospitals which obtain NCI designation within a county

The first variable stepped into the model was number of hospitals in the county affiliated with an AMC. This was chosen because, although patient care is an important component of an NCI CC, generating research funding through collaboration with academic medical institutions is likely a critical factor to obtain NCI designation. This model illustrates that hypothesis 1 of stage 1 is supported; even when all other independent variables are added to the model, concentration of hospitals associated with a academic institutions is a strong predictor of a county having an NCI CC located within its bounds.

Table 15

Logistic regression of likelihood a county has a hospital which obtained NCI designation

Logistic regression of likelihood a county has a hospital which obtained NCI designation

Logistic regression — Number of obs = 2592
Log likelihood = -120.24901 — LR chi2(6) = 245.47; Prob > chi2 = 0.0000; Pseudo R2 = 0.5051

	Model									
NCI in County	1	2	3	4	5	6	SE	P>|z|	[95% CI]	
Hospitals affiliated w/ academic medical centers	1.76 *	1.58 *	1.55 *	1.57 *	1.53 *	1.56 *	.08	.00	1.41	1.73
Large or small metropolitan county		13.39	12.70	11.06	4.82	3.60	2.98	.12	.71	18.22
% Black			5.29	6.77	17.73	8.75 *	10.82	.08	.78	98.81
Education at BS level 45% or more (mean is 17%)				10.02 *	8.10 *	7.02 *	4.87	.01	1.80	27.32
Income over $75,000 above mean (14.%)					4.87 *	4.12 *	2.93	.05	1.02	16.58
Age under 45 above mean (59%)						4.77 *	3.47	.03	1.15	19.82
_cons	.01	.00	.00	.00	.00	.00	.00	.00	.00	.00

Notes: *P<.05, **P<.10

Source: Author's construction

Metropolitan county is a significant factor in the model when you control for race, education, and income. However, once you control for age, metropolitan county is no longer significant because the model has essentially mimicked all the sociodemographic characteristics associated with a metropolitan county. Similarly, when you control for metropolitan county, the percentage of residents that self identify as Black is not significant. Therefore, hypotheses 2 and 3 of the equation 1 of the conceptual model are not supported. Hypotheses 4, 5, and 6 are accepted: When the population has more than 45% of its residents with at least a bachelor degree, more than 14% of it's population has income over $75,000, and more than 59% of its population is under age 45, the county is 21.91 times more likely to have a hospital that obtains NCI designation as a cancer center.

Census socio demographic variables are continuous variables between 0-100 percent. However, these variables are highly intercorrelated. When the logistic regression analysis was conducted, the model became unstable and unreasonable odds ratios were generated. Therefore, these variables were recoded to 0/1 variables to run the model. The 0/1 transformation works because it limits the number of cells in the model. These variables were constructed by obtaining the mean level of the population that had the specific characteristic. The counties which had greater than the mean were coded as 1. For example, for all the counties analyzed, 14% of the population had Income over $75,000. Therefore, this variable was initially recoded as 0/1 with a 1 representing that the county with more than 14% of its population having income greater than $75,000. The same process was applied to age.

I handled the transformation of the education variable differently. Initially, I transformed it to a 0/1 variable based on the mean of 17%. However, the odds ratio remained very high which indicated designation of an NCI cancer center was highly sensitive to education level. To test the sensitivity of this variable, I increased it to as high as 45% of the population. At this level, BS education maintained a statistically significant odds ratio. Therefore, in the NCI analysis, counties with at least 45% of its population with a BS level education, are indicated with a 1. These counties are 7 times more likely to have an NCI CC located within it.

There is some debate about which variable came first. Did high level of education in the county increase the likelihood that an academic medical center obtained NCI

designation or does having an NCI designated cancer center in the county increase the level of education? It is not possible to test it within this study. However, it is worthwhile testing the sensitivity of the education variable.

The final variables that have statistically significant odds ratios are highlighted with a single asterisk for a p-value of less than .05 and a double asterisk for a p-value less than .10. When all the variables are included, model 6, the odds ratios for each significant independent variable can be interpreted in the following manner: For each additional hospital that is affiliated with an AMC, holding all other variables constant, that county has a 56% greater chance of having a hospital that obtained NCI designation. If the county has 45% or more of its population with at least a bachelor degree education, holding all other variables constant, it is 7 times more likely to have a hospital that obtained NCI designation. If the county has more than 14% of its population with income above $75,000, holding all other variables constant, it is 4.12 times more likely to have a hospital that obtained NCI designation. If the county has 59% or more of its population under age 45 years, holding all other variables constant, it is 4.12 times more likely to have a hospital that obtained NCI designation.

Equation 2 Results

Equation 2 tests the likelihood an institution orders the EGFR assay. Of acute care hospitals in the US, 12% (n=592) ordered the EGFR assay. In 49 counties with an NCI designated cancer center (NCI CC), 19% of hospitals ordered the assay, whereas only 11% of hospitals in non NCI counties ordered the assay.

Table 14 illustrates that, as with the NCI CCs, 89% of hospitals ordering the EGFR assay were located within metropolitan counties. These hospitals accounted for 93% of total EGFR assays ordered. 83% of the US population lives within these counties. However, within the large metropolitan counties, the annual incidence of lung cancer is lower than the national mean of 68.75 cases per 100,000 or 158,799 annual cases of lung cancer. There are very few assays ordered in non metropolitan counties, 454 or 7% of total assays. Further, there are 42,550 annual cases of lung cancer in these counties (21% of the lung cancer population), who appear to have little access to the EGFR assay. Table 14 strongly indicates that the disparity that exists in access to the EGFR assay is location within a rural county.

Table 16 summarizes the type of facility, mean rates and distribution of EGFR assays ordered. The mean number of assays ordered from the laboratories and physician offices should be interpreted with caution. The mean for this type of facility is overstated because it does not include all the laboratories and physician offices in the country that did not order the test. However, all acute care, critical access, and federal hospitals are included in the analysis. Therefore, the mean for these types of facilities is accurate.

Table 16

Type of Facility and Mean Rates and Distribution of EGFR Assays

Description	Coded	Obs	Mean	SD	Min	Max
Identifies whether order came from hospital listed in CMS/NCI Provider of Service (POS) dataset.	0 – Hospital	3484	1.74	7.48	0	168
	11 - Critical Access	1296	0.00	0.08	0	2
	1- Lab	60	8.67	13.16	1	55
	2 – Outpatient	48	4.25	6.60	1	29
	3 – VA	161	0.36	1.87	0	16
	4- Military	155	0.23	1.79	0	18
	5 - Other Fed	22	0.00	0.00	0	0
	6 – USPH	22	0.00	0.00	0	0

Notes: Only laboratories that ordered the assay are included in data.
Source: Author's construction

Table 17 summarizes the descriptive statistics of hospital and regional characteristics by status of ordering the EGFR assay. It illustrates that there are 57% (2704) hospitals located within metropolitan counties. Yet, 88% of hospitals that ordered the assay are in metropolitan counties. 56% (2683) of hospitals are in counties with education at BS level above the mean. Yet, 84% of hospitals ordering the EGFR assay are in counties with bachelor degree education level above the mean. 24% (1166) of hospitals have an affiliation with an academic medical center. Yet, 48% of hospitals ordering the EGFR assay are affiliated with an academic medical center. A similar pattern exists with chemotherapy and PET scan services and participation in an NCI cooperative. While only 25% of hospitals in the database offered cardiothoracic surgery, 56% of the institutions ordering the EGFR assay offered cardiothoracic surgery compared to 21% of institutions that did not order the assay. Notice that only 2 of the 1295 Critical Access hospitals ordered the EGFR assay.

Table 17

Descriptive statistics of hospital and regional characteristics by status of ordering the EGFR assay

	All institutions n=4778			Ordered Assay n=592			No Order n=4188		
	sum	mean	sd	sum	mean	sd	sum	mean	sd
Metropolitan county	2704	0.57	0.5	522	0.88	0.32	2182	0.52	0.5
Education at BS level above mean (17%)	2683	0.56	0.5	497	0.84	0.37	2186	0.52	0.5
Affiliation with a Medical School	1166	0.24	0.43	285	0.48	0.5	881	0.21	0.41
Cardiothoracic surgery	1190	0.25	0.43	330	0.56	0.5	860	0.21	0.4
Chemotherapy services	1287	0.27	0.44	236	0.4	0.49	1051	0.25	0.43
PET Scan services	702	0.15	0.35	166	0.28	0.45	536	0.13	0.33
Participated in a NCI Coop	864	0.18	0.38	257	0.43	0.5	607	0.14	0.35
Critical Access Hospital (CAH)	1295	0.27	0.44	2	0	0.06	1293	0.31	0.46

Notes: Only acute care and critical access hospitals included in analysis

Source: Author's construction

The significant difference in means between hospitals that participated in NCI cooperative clinical research groups encouraged me to conduct a separate analysis on each of the cooperative groups to determine whether cooperative groups that participated in EGFR TKI clinical trials were also more likely to order the assay.

Table 18 illustrates the descriptive statistics of NCI cooperative group membership by status of ordering the EGFR assay. NSABP, a surgical clinical research group, had the most number of hospitals participating in the cooperative group. 20% of hospitals that ordered the EGFR assay belonged to NSABP. 15% or 88 hospitals that ordered the assay belong to ECOG. This table illustrates that proportionally, the highest percentage of hospitals ordering the EGFR assay, participated in ECOG (32% of hospitals participating in ECOG ordered the assay), ACOSOG and CALBG had 35% of

its members order the EGFR assay. These cooperative groups were also likely active participants in EGFR TKI clinical trials.

Table 18

Descriptive statistics of NCI cooperative group membership by status of ordering the EGFR assay

	All institutions n=4778			Ordered Assay n=592			No Order n=4188		
	sum	mean	sd	sum	mean	sd	sum	mean	sd
Eastern Co-operative (ECOG)	269	.06	.23	88	.15	.36	181	.04	.20
American College of Surgeons (ACOSOG)	197	.04	.20	70	.12	.32	127	.03	.17
Cancer and Leukemia Group B (CALGB)	154	.03	.18	55	.09	.29	99	.02	.15
Southwest (SWOG)	326	.07	.25	81	.14	.34	245	.06	.23
Radiation Therapy (RTOG)	137	.03	.17	44	.07	.26	93	.02	.15
American College of Radiology (ACRIN)	62	.01	.11	16	.03	.16	46	.01	.10
National Surgical Adjuvant Breast (NSABP)	398	.08	.28	120	.20	.06	278	.07	.25
North Central Cancer Treatment (NCCTG)	150	.03	.17	36	.40	.24	114	.03	.16

Notes: Only acute care and critical access hospitals included in analysis
Source: Author's construction

Although the dependent variable in equation 2 is the hospital, regional characteristics in which the hospital is located are used as independent variables in this equation. Therefore, it is helpful to understand the descriptive statistics of these regional variables. Table 19 illustrates that there are approximately 2 (1.95) hospitals per county. However, many counties have hospitals which are not affiliated with a medical school, do not offer PET scan or cardiothoracic surgery, and do not participate in NCI cooperative groups. The average distance hospitals are from an NCI CC is 137.66 miles. Yet, there are some counties which have hospitals that are 1952.6 miles away from an NCI CC.

The average annual lung cancer cases in counties are 76.31 in 2008. The average annual incidence of lung cancer in the counties is 70.24 per 100,000 people in 2008. In counties with acute care hospitals, 17% of the population has education at least at the

bachelor degree level. 59% of the population is under age 45. 14% of the population has income above $75,000. 9% of the population is Black. 35% of the counties are metropolitan.

Table 19

Descriptive statistics of county level variables

	Obs = 2637 counties			
Hospital characteristics	Mean	SD	Min	Max
Hospitals	1.95	3.29	1	92
Hospitals with a medical school affiliation	.54	1.85	0	36
Hospitals that participate in NCI Coop	.35	1.14	0	24
PET Scan services	.28	.70	0	8
Inpatient chemotherapy	.50	1.08	0	18
Cariothoracic surgery services	.48	1.57	0	34
Distance county centroid is from NCI CC	137.66	123.19	0	1952.6
CDC/NPCR lung cancer data	Mean	SD	Min	Max
Annual cases of lung cancer	76.31	182.08	1	3845
Annual incidence of lung cancer	70.24	21.17	8	262.1
Census county data	Mean	SD	Min	Max
Education at BS level	.17	.41	0	1
Age under 45	.59	.50	0	1
Income over $75,000	.14	.48	0	1
Black	.09	.15	0	.86
Metropolitan county	.35	.48	0	1

Notes: Calculated based on counties with acute care hospitals
Source: Author's construction

Error! Reference source not found. illustrates the logistic regression model. ach variable was stepped into the equation manually to demonstrate the correlation between these variables and the subsequent effect on the dependent model. In model 1, distance to the NCI CC was the first variable stepped in because the central hypothesis was diffusion of the EGFR assay emanates from the NCI cancer centers. The odds rate .991 was generated with a p-value of .00 indicating that for each mile a hospital is away from an NCI, the lower the likelihood it will order the EGFR assay. Next, affiliation with a medical school was stepped in because I hypothesized that these types of hospitals would be early adopters of innovations. Model 2 illustrates that hospitals affiliated with a medical school are 3.12 times more likely to order the EGFR assay, even when controlling for distance to the NCI CC. In model 3, participating in a NCI clinical research cooperative group (Coops) was the third variable stepped in because these hospitals are more likely to have been exposed to the EGFR assay through participation in an EGFR TKI clinical trial. Model 3 illustrates that Coops are 3.13 more likely to order the EGFR assay. However, by stepping in this variable, it decreases the impact affiliating with a medical school has on the dependent variable because many Coops are also likely to be affiliated with a medical school. In model 4, PET scan services was stepped in. Although PET scans are not widely used in treatment of lung cancer, this variable is a proxy for hospitals that are early adopters of technology. Hospitals that offer PET Scan services are 1.89 times more likely to order an EGFR assay.

Table 20

Odds ratio that a hospital ordered the EGFR assay

																4717
Logistic regression														LR chi2(11)	=	648.50
Log likelihood = -1451.7562														Prob > chi2	=	0.0000
														Pseudo R2	=	0.1826
Institution ordered EGFR assay	1	2	3	4	5	6	7	8	9	10	11	SE	z	P>|z|	[95% CI]	
Distance to NCI CC	.992	.993	.994	.994	.994	.994	.996	.996	.996	.996	.996	.00	-5.32	.00	1.00	1.00
Affiliated w/ academic medical center		3.13	2.25	2.11	1.67	1.67	1.55	1.48	1.50	1.48	1.48	.16	3.63	.00	1.20	1.83
NCI clinical research cooperative			3.13	2.96	2.31	2.32	2.14	2.08	2.06	2.06	2.06	.22	6.62	.00	1.66	2.55
Pet scans				1.89	1.50	1.41	1.41	1.44	1.44	1.44	1.44	.22	2.41	.02	1.07	1.94
Cardiothoracic surgery					2.62	2.60	2.00	1.91	1.90	1.90	1.90	.21	5.72	.00	1.52	2.37
Inpatient chemotherapy*						1.09	1.16	1.15	1.15	1.15	1.15	.16	1.05	.30	.88	1.50
Within metropolitan county							3.00	2.42	2.11	2.07	2.08	.36	4.26	.00	1.48	2.91
Education at BS level above mean (17%)								1.66	1.46	1.45	1.46	.22	2.50	.01	1.09	1.96
Income over $75,000 above mean									1.44	1.46	1.46	.25	2.19	.03	1.04	2.05
% Black*										1.29	1.30	.48	.71	.48	.63	2.67
Annual lung cancer cases											1	.00	-0.18	.86	1	1
_cons	.30	.18	.14	.13	.11	.11	.05	.04	.03	.03	.03	.01	-19.47	.00	.02	.05

* P>.05

Notes: Most variables were significant therefore p-value of greater than .05 have an asterisk.
Source: Author's construction

PET Scan services also decreased the impact medical school affiliation and participation in a cooperative group had but did not change the influence distance had on the likelihood of ordering the EGFR assay. Model 5 stepped in the variable cardiothoracic surgery services. Hospitals that offer cardiothoracic surgery are most likely to conduct lung cancer surgery and therefore likely to have more lung tumor tissue available for conducting the EGFR assay. This hypothesis was supported. Hospitals that offer cardiothoracic surgery are 2.61 times more likely to order the assay. However, there is clearly some correlations between these hospital characteristics because the influence of medical school affiliation, participating in an NCI cooperative group, and offering PET scan services decreases when cardiothoracic surgery is added. All hospital characteristics except chemotherapy services remain significant predictors of ordering the EGFR assay. Model 6 steps in inpatient chemotherapy services. This variable is not statistically significant. Although inpatient chemotherapy services is an indicator of offering advanced cancer care services, the effect of this variable is likely being captured by the previous characteristics. Hospitals that affiliate with a medical school, participate in NCI cooperative groups, offer PET scan and cardiothoracic surgery, are also likely to offer chemotherapy services. In model 7, I stepped in the regional variable of location within a metropolitan county. As illustrated, when controlling for all other variables, location within a metropolitan county is a significant predictor of ordering the EGFR assay. Model 8 steps in the education level of the county. When controlling for distance to the NCI CC, all the institutional characteristics, and location within a metropolitan county,

hospitals located within counties that have more than 17% of their population educated at least the bachelor's degree level, are more likely to order the EGFR assay. Model 9 illustrates that the percentage of Blacks within a county is not a significant predictor of whether the hospital orders the EGFR assay. As was illustrated in equation 1, hospitals that order the EGFR assay may be located in urban metropolitan communities that have a high minority population. Therefore, hypothesis 7 is not supported. Model 10 tests hypothesis 9, whether, controlling for distance, institutional characteristics, and other regional characteristics, a hospital located in a high income county is more likely to order the EGFR assay. This hypothesis is supported. Controlling for all other variables, hospitals located in counties that have more than 14% of its population with income above $75,000 are 1.46 times more likely to order the EGFR assay.

Model 11 stepped in the annual number of lung cancer cases in the county. In an equitable and rational healthcare system, this variable would be the biggest causative factor driving both the number of EGFR assays ordered as well as the number of hospitals ordering the assay. However, as model 11 illustrates, this is not a statistically significant factor in whether a hospital orders the EGFR assay.

Other than hypotheses 1 and 7, all hypotheses in equation 2 are supported. Neither number of lung cancer cases or percentage of Blacks living in a county had a statistically significant effect on whether a hospital ordered the EGFR assay.

Hospital and regional characteristics had the hypothesized effect on likelihood a hospital would order the EGFR assay. Significant institutional predictors of ordering the

assay included: Participation in an NCI clinical research cooperative group (odds ratio [OR], 2.06, 95% CI 1.66 to 2.55), Cardiothoracic Surgery (OR, 1.90; 95% CI, 1.52 to 2.37), PET Scan services (OR, 1.44, CI, 1.07 to 1.94), and affiliation with academic medical center (OR, 1.48; 95% CI, 1.20 to 1.83). Inpatient chemotherapy services were not statistically significant once all other institutional characteristics were stepped in. Significant regional predictors included: metropolitan county (OR, 2.08; 95% CI, 1.48 to 2.91), education above the mean (OR, 1.46; 95% CI, 1.09 to 1.96), and income above the mean (OR, 1.46; 95% CI, 1.09 to 1.96). Negative predictors were distance from an NCI CC (OR, .996, 95% CI, .995 to .998), a 34% decrease in likelihood for every 100 miles further from an NCI CC.

It is worth discussing hypothesis 5, distance to a comprehensive cancer center, in greater depth. The hypothesis was that distance between the hospital and an NCI CC will have an inverse relationship to the likelihood the institution ordered the EGFR assay. When this variable is initially stepped in, the odds ratio is lower than 1 and the p value is statistically significant. However, once other variables are stepped in, the odds ration gets closer and closer to 1 yet remains statistically significant. This is explained by the fact that distance is a continuous variable measured as each mile the hospital is from the NCI CC. With the exception of percentage Black, all other variables are measured as categorical 0/1 variables.

The model was rerun in logit to obtain a coefficient for distance rather than an odds ratio. The logit coefficient generated was -.00411 when the model was run on

institutions in non-NCI counties. I multiplied this by 100 miles and exponentiated which gave us a the value of .663. For every 100 miles further from an NCI CC, the likelihood of a hospital ordering the EGFR assay decreases by 34%. When hospitals in all counties were analyzed,for every 100 miles further from an NCI CC, the likelihood of ordering an EGFR assay decreases by 24%. This variable may have a non linear relationship with the dependent variable.

Sensitivity Testing of Equation 2 Results

In the methods section, there was some discussion about the possibility that the strength of the odds ratios may be overestimated given the low number of institutions ordering the EGFR assay and the limited number of counties in which these institutions operate. The sensitivity of the model was tested in a number of different ways. Table 21 illustrates that when characteristics of just the 1662 hospitals located within the 383 counties in which at least one hospital ordered an EGFR assay, the variables that remain significant are: participation in an NCI cooperative group and offering cardiothoracic surgery. Distance to a comprehensive cancer center and inpatient chemotherapy services are significant at a p-value of .10. In this analysis, annual lung cancer cases become a significant negative predictor of ordering the assay. When rounded, the odds ratio and confidence intervals become 1. The regional variables are not included because by limiting the analysis to hospitals in the 383 EGFR counties, the effects of education, income, and metropolitan county are captured within the EGFR county constraint.

Table 21

Odds ratios of hospitals located within 383 EGFR assay counties

Hospitals within counties that have at least 1 EGFR assay ordered

	Number of obs	= 1662
Logistic regression	LR chi2(11)	= 147.11
Log likelihood = -1006.9484	Prob > chi2	= 0.0000
	Pseudo R2	= 0.0681

Institution ordered EGFR assay	OR	SE	z	P>|z|	[95% CI]	
Distance to NCI CC	.999	.001	-1.700	.089	.998	1.000
Affiliated w/ academic medical center	1.11	.13	.90	.37	.88	1.401
NCI clinical research cooperative*	1.88	.23	5.22	.00	1.48	2.377
Pet scans	1.21	.21	1.10	.27	.86	1.705
Cardiothoracic surgery*	1.53	.18	3.60	.00	1.21	1.936
Inpatient chemotherapy	1.30	.20	1.72	.09	.96	1.765
Annual lung cancer cases*	1.00	.00	-6.01	.00	1.00	1
_cons	.46	.05	-6.85	.00	.37	0.573

* P<.05

Notes: Fewer variables were significant therefore p-value of less than .05 have an asterisk.
Source: Author's construction

Another method of testing the sensitivity of the institutional characteristic and distance variables is to conduct an analysis of hospitals located outside NCI counties compared to within NCI counties. Tables 22 and 23 are the logistic regression models conducted by whether hospitals are located within NCI counties. All but 2 NCI CCs are located within metropolitan counties, therefore the regional variables were excluded from table 23 but included in table 22. As illustrated in table 22, there are 4,179 hospitals located non-NCI counties. All variables except percent Black and inpatient chemotherapy were statistically

Table 22

Odds ratios of hospitals located outside NCI counties

Hospitals within counties that have at least 1 EGFR assay ordered

				Number of obs	=	4179
Logistic regression				LR chi2(11)	=	592.46
Log likelihood = -1175.3463				Prob > chi2	=	0.0000
				Pseudo R2	=	0.2013
Institution ordered EGFR assay	OR	SE	z	P>|z|	[95% CI]	
Distance to NCI CC	.996	.001	-5.080	.000	.995	.998
Affiliated w/ academic medical center	1.54	.19	3.54	.00	1.21	1.95
NCI clinical research cooperative	2.07	.25	5.89	.00	1.62	2.63
Pet scans	1.72	.29	3.25	.00	1.24	2.38
Cardiothoracic surgery	1.56	.20	3.49	.00	1.22	2.01
Inpatient chemotherapy*	1.07	.16	.43	.67	.79	1.43
Within metropolitan county	1.70	.30	2.98	.00	1.20	2.42
Education at BS level above mean (17%)	1.39	.22	2.10	.04	1.02	1.88
Income over $75,000 above mean (14.34%)	1.67	.32	2.64	.01	1.14	2.43
% Black*	1.09	.49	.20	.85	.46	2.61
Annual lung cancer cases	1.00	.00	5.10	.00	1.00	1.00
_cons	.03	.01	-18.55	.00	.02	.05

* P>.05

Notes: Most variables were significant therefore p-value of greater than .05 have an asterisk.

Source: Author's construction

significant in this model which suggests that, even with all the zeros in the analysis, the model is somewhat robust.

Table 23 limits the analysis to the 538 hospitals located within 49 NCI counties. This analysis illustrates the strength of the variables participating in an NCI clinical research cooperative and offering cardiothoracic surgery. The statistically significant odds ratios for the various models are compared in Table 24. While the regional variables

Table 23

Odds ratios of hospitals located within 49 NCI counties

Hospitals within counties that have at least 1 EGFR assay ordered

Number of obs = 538
Logistic regression — LR chi2(11) = 70.66
Log likelihood =-247.68936 — Prob > chi2 = 0.0000
Pseudo R2 = 0.1248

Institution ordered EGFR assay	OR	SE	z	P>|z|	[95% CI]	
Distance to NCI CC	.998	.002	-1.150	.249	.994	1.002
Affiliated w/ academic medical center	1.06	.27	.22	.83	.64	1.735
NCI clinical research cooperative*	2.15	.53	3.10	.00	1.33	3.48
Pet scans	.89	.37	-.27	.79	.40	1.997
Cardiothoracic surgery*	4.29	1.12	5.59	.00	2.58	7.155
Inpatient chemotherapy	.98	.33	-.06	.95	.51	1.879
Annual lung cancer cases	1.00	.00	-1.12	.26	1.00	1.00
_cons	.11	.03	-8.37	.00	.06	0.182

* P<.05

Notes: P-value of less than .05 have an asterisk.
Source: Author's construction

would likely still be statistically significant, it is not possible to measure that when the analysis is restricted to EGFR and NCI counties because these are by default metropolitan counties, often with higher education and income levels.

Table 24 illustrates that when the analysis is restricted to a very select number of hospitals in NCI counties, the most significant predictor of whether that hospital orders the EGFR assay is whether it conducts cardiothoracic surgery. This is perhaps best explained by the fact that those hospitals are more likely to have thoracic surgeons who

may be more informed about lung cancer molecular diagnostics. Further, there is more tissue available to analyze when surgery is conducted rather than a fine needle aspirate.

Table 24

Comparison of odds ratios when analysis is restricted by counties

	Table 20	Table 21	Table 22	Table 23
	Full model	383 EGFR	2539 Non NCI	49 NCI
	OR	OR	OR	OR
Distance to NCI CC	.996		.996	
Affiliated w/ academic medical center	1.48		1.54	
NCI clinical research cooperative	2.06	1.88	2.07	2.15
Pet scans	1.44		1.72	
Cardiothoracic surgery	1.90	1.53	1.56	4.29
Inpatient chemotherapy				
Within metropolitan county	2.08		1.70	
Education at BS level above mean (17%)	1.46		1.39	
Income over $75,000 above mean (14.34%)	1.46		1.67	
P-value <.05				

Notes: OR of variables with p-value of less than .05
Source: Author's construction

Across all models, participating in an NCI clinical research cooperative group remained a strong predictor of the institution ordering the EGFR assay. Within jus the 383 EGFR counties, Coop hospitals are 1.88 times more likely to order the assay compared to non Coop hospitals. Within the 538 hospitals that are located within NCI counties, Coop hospitals are 2.15 times more likely to order the EGFR assay. When this analysis is expanded to all hospitals nationally, Coop hospitals are still 2.06 times more

likely to order the assay. The strength of this variable is explained by the fact that these hospitals are more likely to have participated in EGFR TKI clinical trials. Therefore, their providers have experience ordering the assay for patients. Or, hospitals that participate in NCI clinical research cooperatives may have oncologists that are more informed about the diagnosis and treatment of cancer patients based on the molecular biology of the tumor.

Another sensitivity test distinguishes the influence of different NCI clinical research cooperative groups. Does participation in specific groups increase the likelihood the hospital ordered the EGFR assay? **Error! Reference source not found.** illustrates hat cooperative groups that offer lung cancer clinical trials (ECOG, CALGB, ACOSOG) were statistically significant with odds ratios between 1.70 to 2.11.

Table 25

Odds ratio that a hospital ordered an EGFR assay by cooperative group participation

Hospitals within counties that have at least 1 EGFR assay ordered

				Number of obs	=	4717
Logistic regression				LR chi2(11)	=	650.25
Log likelihood = -1450.8851				Prob > chi2	=	0.0000
				Pseudo R2	=	0.1831

Institution ordered EGFR assay	OR	SE	z	P>|z|	[95% CI]	
Distance to NCI CC*	.996	.001	-5.060	.000	.995	.998
Affiliated w/ academic medical center*	1.50	.16	3.74	.00	1.21	1.86
Eastern Co-operative (ECOG)*	1.70	.30	3.00	.00	1.20	2.41
American College of Surgeons (ACOSOG)*	1.74	.33	2.87	.00	1.19	2.54
Cancer and Leukemia Group B (CALGB)*	2.11	.43	3.63	.00	1.41	3.15
Southwest (SWOG)	1.18	.20	.97	.33	.85	1.63
Radiation Therapy (RTOG)	1.20	.27	.82	.41	.77	1.87
American College of Radiology (ACRIN)	.92	.36	-.20	.84	.43	1.99
National Surgical Adjuvant Breast (NSABP)	1.15	.19	.85	.40	.84	1.58
North Central Cancer Treatment (NCCTG)	.79	.19	-.96	.34	.49	1.28
Pet scans*	1.41	.22	2.24	.03	1.04	1.90
Cardiothoracic surgery*	1.95	.22	5.91	.00	1.56	2.43
Inpatient chemotherapy	1.15	.16	1.06	.29	.88	1.50
Within metropolitan county*	2.10	.36	4.30	.00	1.50	2.94
Education at BS level above mean (17%)*	1.50	.23	2.67	.01	1.11	2.01
Income over $75,000 above mean (14.34%)*	1.47	.26	2.22	.03	1.05	2.07
% Black	1.17	.44	.42	.68	.56	2.43
Annual lung cancer cases	1.00	.00	-.17	.87	1.00	1.00
_cons	.03	.01	-19.27	.00	.02	.05

P-value<.05*

Notes: P-value of less than .05 have an asterisk.
Source: Author's construction

Equation 3 Results

There are several differences between equation 2 and equation 3. The most significant difference is the dependent variable. In equation 2, the dependent variable was a dichotomous variable (0 or 1) which measured the likelihood a hospital ordered an EGFR assay. The model used logistic regression analysis. The independent variables were regional and hospital characteristics. In equation 3, the dependent variable is the number of EGFR assays ordered by hospitals within a county divided by the number of guideline directed lung cancer cases in that county. It is calculated as a rate between 0 and 1, with 0 indicating that no hospitals within the county ordered the assay and 1 indicating that that the number of assays ordered by all hospitals in the county was equal to the number of guideline directed lung cancer cases. Because the EGFR rate is a continuous variable, the model will use multiple regression to analyze the independent variables rather than logistic regression. Independent variables in the model are county level sociodemographics and county level hospital characteristics. The first thing to note about the model is that there are a large number of counties that have zero utilization. There are 2496 counties in the dataset. 383 counties had an EGFR rate greater than 0 and 2,113 counties that had a utilization rate of 0. The large number of counties with 0 utilization will cause the effect size of any of the regression coefficients to be small. It will also decrease the slope of the linear regression.

It is worth noting that by excluding data from NCI CCs, the utilization rate nationally and within the counties in which the NCI CC is located, will be artificially

suppressed. One test of sensitivity is to conduct a separate analysis on the 383 counties which had greater than 0 utilization.

Table 26 presents the results of the multiple regression of all 2496 counties.

Table 26

Multiple regression of EGFR rate for all counties with acute care hospitals

Source	SS	df	MS
Model	.6036	8	.0755
Residual	6.06	2483	.0024
Total	6.6667	2491	.0027

Number of obs =2492
F(8, 2483) = 30.9
Prob > F = 0
R-squared = .095
Adj R-squared=.0876
Root MSE = .0494

EGFR Rate	Coeff	SE	z	P>|z|	[95% CI]	
Distance to NCI CC*	-.001	.001	-2.410	.016	-.002	.000
Affiliated w/ academic medical center	.002	.001	1.420	.155	-.001	.005
NCI clinical research cooperative*	.006	.002	3.100	.002	.002	.009
Pet scans*	.010	.002	5.420	.000	.006	.013
Cardiothoracic surgery*	-.002	.001	-1.930	.054	-.005	.000
Education at BS level*	.103	.019	5.290	.000	.065	.141
Income over $75,000	-.017	.020	-.850	.396	-.057	.023
Black	.006	.007	.810	.417	-.008	.019
_cons	-.007	.003	-2.360	.018	-.012	-.001

P-value<.05*

Notes: P-value of less than .05 have an asterisk.
Source: Author's construction

The distance the county is to an NCI cancer center, the number of hospitals in the county that participate in an NCI cooperative group, offer PET scan services, and the education level of the county are all statistically significant. These coefficients can be interpreted in the following manner: Holding everything else constant, for every 100 miles the county is from a county with an NCI cancer center, the EGFR rate decreases by .001. For every

hospital in the county that participates in an NCI clinical research cooperative group, the EGFR rate increases by .006. For every hospital in the county that offers PET scan services, the EGFR rate increases by .01. And, for each percentage of the population that had at least a bachelor degree education, the EGFR rate increases by .103. Education level of the county had the strongest influence on the EGFR rate. Although the influence these variables have on the EGFR rate seems so small that it is insignificant, the mean EGFR rate is .016. Therefore, the influence of these variables is not as insignificant as it may seem.

Although the number of hospitals in the county offering cardiothoracic surgery was not statistically significant at .05, it was significant at a p value of .10. However, the direction of influence on the EGFR rate was negative. When the number of hospitals in a county offering cardiothoracic surgery was analyzed independently, it had a positive coefficient of .007 with a p-value of .000. Therefore, holding other variables constant, particularly the number of hospitals in a country that offer PET scan services and participate in NCI clinical research cooperatives may be masking the effect of cardiothoracic surgery.

A test of sensitivity of the model was conducted by limiting analysis of the independent variables on the EGFR rate for the 383 counties that had a rate of greater than 0. Table 27 is the multiple regressions of these 383 counties.

Table 27

Multiple regression of EGFR rate for counties with greater than zero utilization

Source	SS	df	MS
Model	1.219	8	.152
Residual	44.23	373	.118
Total	45.45	381	.119

Number of obs =383
F(8, 2483) = 1.29
Prob > F = .2495
R-squared = .0268
Adj R-squared=.006
Root MSE = .34437

EGFR Rate	Coeff	SE	z	P>|z|	[95% CI]	
Distance to NCI CC	.006	.017	.340	.731	-.028	.040
Affiliated w/ academic medical center*	.028	.014	2.040	.042	.001	.055
NCI clinical research cooperative	-.026	.016	-1.570	.118	-.058	.007
Pet scans	-.010	.017	-.560	.577	-.044	.024
Cardiothoracic surgery	-.011	.011	-1.050	.296	-.032	.010
Education at BS level	.388	.315	1.230	.218	-.230	1.007
Income over $75,000**	-.536	.315	-1.700	.090	-1.155	.083
Black**	-.233	.141	-1.650	.100	-.510	.045
_cons	.169	.058	2.920	.004	.055	.282

P-value<.05*
P-value<.10**

Notes: P-value of less than .05 has one asterisk. P-value of .10 has two asterisks.
Source: Author's construction

There are three statistically significant variables: Number of hospitals in a county affiliated with an academic medical center, the percentage of the population within the county that has income over $75,000 and that self identify as Black. The number of hospitals in a county affiliated with an academic medical center and the percentage Black had the expected effects. For each additional hospital in a county affiliated with an academic medical center, the EGFR rate increases by .028. For each percentage point increase in the number of Blacks within the county, the EGFR rate decreases by .233.

However, for each percentage increase in the number of people reporting income over $75,000, had a decrease in the EGFR rate by .536. This variable may indicating that lung cancer patients that live in counties which have high incomes may be more likely to travel outside their county to obtain care at an NCI cancer center, where the EGFR assay utilization rate is not captured in this model. Alternatively, it could indicate that counties with high income also have lower smoking rates and lower numbers of lung cancer cases. However, this should be capturing in the EGFR rate.

There are several factors that need to be noted about this model. The R-squared is very low in both analyses. The model in Table 26, all counties with acute care hospitals, explains .095% of the EGFR utilization rate. Table 27, the model analyzing just the counties with greater than 0 utilization rate, explained approximately 3% of the model. This indicates that the independent variables taken together are a weak predictor of the EGFR utilization rate, despite having a statistically significant p values. This is not entirely unexpected given the lack of data from NCI CCs, the underutilization of the assay overall, and the fact that lung cancer incidence, which should be the most significant causal factor, was not statistically significant.

CHAPTER 5

Conclusions and implications

The primary objectives of this analysis were to:

1) Identify institutional and regional factors that contributed to the adoption and utilization of the EGFR assay. Equation 2 of the model measured adoption of the EGFR assay. It was the most successful model demonstrating that several hypothesized institutional characteristics were predictors of the EGFR assay. These include an institution participating in an NCI clinical research cooperative group, offering cardiothoracic surgery, chemotherapy, and PET scan services, and affiliation with an academic medical center. Distance to an NCI CC was a statistically significant variable but the negative effect it had on likelihood the institution ordered the EGFR assay was not as strong as originally hypothesized. From a policy perspective, the most interesting finding related to this objective was the success that the NCI clinical research cooperative groups appear to have in diffusion knowledge from the NCI CC to the surrounding communities.
2) Elucidate structural factors that may contribute to differences in access to this technology. This analysis clearly illustrated that institutions operating within non metropolitan counties are unlikely to order the EGFR assay. This finding should be investigated when patient level data is analyzed to determine whether patients with lung cancer who live in non metropolitan counties are obtaining lower quality lung

cancer care. Another structural factor illustrated in this analysis is that counties with a higher percentage of residents with college education are more likely to have an NCI CC located within their boundaries and are also more likely to have an institution that has ordered the EGFR assay, even when all other variables are factored in the model. These findings are consistent with many of the recent findings by the Dartmouth Atlas group discussed in the background and systematic review.

3) Examine potential implications that differential rates of adoption have for poor and minority NSCLC patients. As mentioned in the methodological challenges, one of the challenges in conducting any geographic analysis of healthcare utilization is that patients, particularly those with serious illnesses, may cross geographic boundaries to seek better care. Furthermore, when the data is at the institutional and county level, it is not really possible to draw conclusions about patient level variables. Given that NCI CCs locate in metropolitan counties that have large minority populations living in the urban centers, without analyzing patient level data, it is impossible to prove that Blacks are not getting access to the EGFR assay, even if there is a strong indication in the clinical trials literature. These methodological problems underscore the importance of conducting an analysis of patient access to lung tumor genotyping using the Medicare claims data. The vast majority of lung cancer patients are Medicare patients. Therefore, analysis of the 331,000 lung cancer patients Medicare claims file will provide a comprehensive analysis of quality of lung cancer care and variable driving access to personalized cancer care.

4) One of the most significant findings of this analysis was that the low utilization rate of the EGFR assay indicates a lack of implementation of evidenced based guidelines. ASCO and NCCN guidelines recommend tumors of certain lung cancer patients to be analyzed for an EGFR mutation. Nursing, as administrators, educators, researchers, policy analysts, and patient advocates play an important role in encouraging institutions in which they work to implement and follow evidence based clinical practice guidelines. The increasing complexity of cancer genomics and the pace of changes make it difficult for oncologists, who are already overburdened and facing a shortage, to be adequately and fully informed about the most recent changes in guidelines surrounding molecular diagnostic tests. Advanced practice and oncology nurses will be playing an increasingly important role in helping patients get the highest quality care possible. Care that is based on evidence not anecdotal beliefs. By understanding the process of diffusion, nursing will be in a unique position to benefit patients and the profession by considering innovations in the profession that will solve some of the problems associated a shortage of oncologists, particularly in non metropolitan counties.

It appears as though Genzyme Genetics took a traditional approach toward marketing the EGFR assay through physician channels. Given the role of physicians as agent to the patient, this was probably the path most companies would have taken. However, when physicians are reluctant to change practice patterns, even in the face of evidence based guidelines encouraging them to do so, incrementalism may stop being the

most effective approach. When patients and their advocates are educated and informed about innovations, it may result in faster, more disruptive innovation – particularly if there are strong patient advocate groups like the breast cancer advocate groups.

There are no regulatory or reimbursement barriers that explain the slow and inadequate diffusion of the EGFR assay. There appears to be either a lack of knowledge about the innovation, among oncologists and surgeons, in addition to a lack of adherence to clinical practice guidelines outlining the best steps to diagnosis and treat lung cancer patients. This analysis suggests that only 15% of lung cancer patients are benefitting from this important advance in the diagnosis and treatment of lung cancer.

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