D. Proposal: Understanding and Promoting Best Practices in Molecular Testing for Non-small Cell Lung Cancer Patients in Florida

I. Overall Aim and Objectives:

Recent advances in the molecular characterization of non-small cell lung cancer (NSCLC) have resulted in FDA-approved therapies targeting molecular abnormalities in the epidermal growth factor receptor (EGFR) and the anaplastic lymphoma kinase (ALK) genes. Identification of these molecular abnormalities in tumor tissue and implementation of appropriate targeted therapies has resulted in clinically meaningful improvements in outcomes for subpopulations of NSCLC patients.[1-6] As a result, evidence-based practice guidelines recommend molecular testing of tumor specimens to inform treatment of NSCLC patients.[7-9] While this rapid shift in recommended practices offers significant promise for the future, multiple studies have identified both gaps in knowledge and barriers to implementing best practices for molecular testing. While the majority of oncologists report discussing molecular testing with their patients, physicians identify multiple barriers to testing, including costs, tissue acquisition and delays in initiating treatment.[10] Furthermore, only 12% of lung cancer patients surveyed recently through the National Lung Cancer Partnership (NLCP) indicated that their tumor tissue had undergone molecular testing.

Approximately 50% of adenocarcinomas will harbor an actionable mutation and recent data on squamous cell carcinomas reflects a similar paradigm.[11] The complexity of testing and treatment for lung cancer patients will only increase as additional mutations and therapies are identified. In order to provide optimal patient care in this rapidly changing landscape, it is crucial to develop reliable processes now for performing, reporting and utilizing molecular testing in patients with lung cancer. With the broad aims of improving care for lung cancer patients in Florida and building a solid foundation for molecular testing in the future, the specific aims of this project are to:

1. Evaluate current practices and barriers to lung cancer molecular testing in the state of Florida; and
2. Develop sustainable and comprehensive practices through the Florida Initiative for Quality Cancer Care (FIQCC) network to ensure access to molecular testing and appropriate targeted therapy for patients with advanced lung cancer.

II.   Technical Approach:

This project will assess and improve molecular testing for lung cancer patients on a systems level. We will utilize the substantial infrastructure of the FIQCC to harness the expertise of all the stakeholders involved in the testing and treatment of lung cancer patients, including oncologists, surgeons, radiologists, pathologists, pulmonologists, oncology nurses and patients. Our intervention will be aimed at all of these stakeholders and determination of the success of our intervention will involve assessment of all of these stakeholders.

a.   Current Assessment of Need in Target Area

Florida has the second highest death rate from cancer in the United States.[12] Since 1999, the Moffitt Cancer Center & Research Institute, an NCI-designated Comprehensive Cancer Center, has been developing affiliations with strategically located hospitals and practices throughout Florida. Over the past eight years, the Moffitt Affiliate Network has grown to include 17 community hospitals and more than 280 affiliated oncologists. It is estimated that, currently, upwards of 20% of all cancer patients in Florida are treated by network members. The Department of Thoracic Oncology at Moffitt evaluates approximately 1200 patients with a new diagnosis of lung cancer annually. With this large patient base and our interaction with referring physicians and affiliates, our team has firsthand experience with the challenges and opportunities facing physicians in implementing personalized medicine for lung cancer patients in Florida. Based on our own experience and a review of the literature, we have identified multiple areas of need, where optimal patient care around molecular testing may be improved. These include:

1.   Gap: Collection of sufficient tissue for molecular testing at initial biopsy.

The majority of patients with lung cancer present at an advanced stage, where palliative rather than curative therapy must be pursued.[13] As such, evaluation of patients with a suspected diagnosis of advanced lung cancer has long focused on acquiring tissue in the most rapid and safe manner possible. With the goal of obtaining tissue mainly for the purpose of confirming malignancy and differentiating non-small cell from small cell lung cancer, small cytologic specimens and less invasive biopsy techniques became the norm. While our knowledge of how to optimally select therapy based on histology and tumor molecular markers has advanced, our ability to obtain sufficient tissue to make these treatment decisions lags behind. When cytologic specimens are used, experienced pathologists achieved a diagnostic accuracy of only 50% for adenocarcinomas and 75% for squamous cell carinomas.[14] Indeed, even in the controlled setting of clinical trials with tissue acquisition as a goal, obtaining sufficient tissue for molecular studies remains a challenge, with recovery rates of viable tumor samples typically less than 50% across multiple clinical trials.[2, 15-19]

Our experience has reflected the challenges reported in the literature with respect to tissue acquisition. The majority of patients eventually evaluated at Moffitt undergo an initial biopsy for suspected lung cancer *prior to* evaluation by a medical oncologist or a multidisciplinary team (Pinder-Schenck M, unpublished data). Initial biopsies frequently yield insufficient tissue for molecular testing and additional biopsies are required, thereby delaying appropriate treatment and putting the patient at additional risk. Pulmonologists, surgeons and interventional radiologists, the providers most likely to perform a biopsy for a diagnosis of lung cancer, receive insufficient training on tissue requirements and the importance of molecular testing. Inadequate communication

amongst providers regarding biopsy requirements or a lack of involvement of key stakeholders in the process can lead to insufficient or improperly collected tissue.[20]

Metric: Adequate tumor tissue will be collected and molecular testing performed at the time of initial biopsy for a diagnosis of advanced NSCLC.

Our baseline analysis of current practices at Moffitt and affiliate sites through the Florida Initiative for Quality Cancer Care (FIQCC) (phase 1) will be compared to practices post-intervention (phase 4) to determine whether a significant increase in collection of adequate tumor tissue for molecular testing at diagnosis has occurred. These data will be obtained through chart review as described in our study design and methods below.

2.   **Gap: Delays in testing and treatment.** In the United States, an initial biopsy often occurs outside the institution where a patient is ultimately treated. This can lead to delays or errors in performing molecular testing. Delays which impact patient care can occur at multiple steps in the process: deciding which patients should undergo molecular testing, transferring tissue from one institution to another for molecular testing; communication between the treatment team and the pathologist regarding which tests need to be completed; reporting of results to the treatment team; and implementation of appropriate treatment in response to results. Selected institutions have, however, reported the feasibility of obtaining tissue and performing molecular testing with a turnaround time that is reasonable for clinical decision-making.[21, 22] It is our intention to evaluate current turnaround times from date of biopsy to date of order placed for molecular testing to date of reporting of results and from date of reporting to date of initiation of therapy for patients with non-small cell lung cancer treated at Moffitt and affiliate sites. The goal of our intervention will be to bring these turnaround times in line with those reported as best practices in the above referenced studies.

Metric: Results of molecular testing will be communicated in a timely fashion to members of the treatment team and will inform treatment decisions early in the course of a patient's treatment for advanced NSCLC.

Our baseline analysis will document current turnaround times for molecular testing and implementation of therapy for patients diagnosed with advanced NSCLC at Moffitt and affiliate sites. These data will be compared to post-intervention turnaround times to assess the effectiveness of our intervention, with a goal of decreasing turnaround times to a timeframe that allows real-time clinical decision-making. Exact time frames to be targeted post-intervention will be determined by stakeholders at the annual FIQCC meeting.

3.   **Gap: Insufficient education of patients and involvement in decisions around molecular testing.** A minority of patients with NSCLC reported having a discussion of molecular testing with a member of their treatment team or being informed regarding results of molecular testing. Furthermore, oncology nurses, who are pivotal in educating

patients regarding test results and treatment options, reported a lack of knowledge and resources to equip them to educate patients regarding molecular testing and targeted treatment. To ensure the best outcomes, patient involvement and education are crucial at multiple steps in the process, from obtaining adequate biopsy specimens to ensuring adherence with oral medications.

Metric: Patients with advanced NSCLC will receive education regarding molecular testing and its importance in determining treatment and shaping outcomes. Our baseline analysis will assess documentation in the medical record of patient education around molecular testing results. One component of our approach to improve molecular testing practices will involve inclusion of patient advocates at the FIQCC meeting to determine how to best involve patients in decision-making around molecular testing. Our post-intervention analysis will compare documentation of patient education around molecular testing to baseline practices.

b. Intervention Design and Methods
This project will assess and improve molecular testing for lung cancer patients on a systems level. We will utilize the substantial infrastructure of the FIQCC to harness the expertise of all the stakeholders involved in testing and treatment of lung cancer patients, including oncologists, surgeons, radiologists, pathologists, pulmonologists, oncology nurses and patients. We will accomplish our objectives in four stages, which are described in detail below:

Stage 1. Medical record review at FIQCC sites to establish baseline practices and to identify systems and site-specific gaps.

Case Selection
Inclusion Criteria

At Moffitt, a random sample of 100 patients with a diagnosis of stage IV non-small cell lung cancer will be selected from amongst all patients with stage IV non-small cell lung cancer first evaluated by a medical oncologist in 2012. Random samples of 50 patients will be selected at each affiliate site from amongst all patients evaluated at that site for a diagnosis of stage IV non-small cell lung cancer.

Exclusion Criteria
Patients under the age of 18
Patients who present with multiple primary cancers (excluding basal cell carcinoma)
Patients seen for follow-up, transfer of care, or second opinion
Mixed non-small cell and small cell carcinoma
Small cell carcinoma
Carcinoid tumor
Adenoid cystic carcinoma

Study Variables

Quality indicators have been determined through our review of guidelines, literature and gap analysis as described above in section A1-3. These are listed below:

1. Was there evidence in the medical chart confirming that a biopsy was performed for suspected lung cancer?
2. Was there evidence of a pathology report with results of the biopsy in the medical chart?
3. What was the time elapsed between a suspected diagnosis of lung cancer and performance of a biopsy?
4. What type of biopsy was performed and by whom?
5. Was there evidence in the chart of a request or intention to perform molecular testing?
6. If molecular testing was requested, which tests were requested?
7. Was a report of molecular testing results in the medical chart?
8. What was the time elapsed between time of biopsy and reporting of results of molecular testing?
9. Was a second biopsy performed in cases where insufficient tissue was available for molecular testing?
10. Was there evidence in the medical chart documenting a discussion of molecular testing with the patient?
11. Was there evidence in the medical chart documenting that results of molecular testing were shared with the patient?
12. What was the time elapsed between biopsy for suspected lung cancer and initiation of systemic therapy?
13. For patients found to have EGFR mutations, was erlotinib started as first-line therapy?
14. For patient found to have ALK translocations, was crizotinib started as first-line therapy?

Additional data to be collected on all cases includes:

- Date of chart review
- Abstractor name
- Participating site name
- Patient gender
- Patient age
- Patient race/ethnicity
- Patient payor status

Data Collection Procedures

Data elements will be collected retrospectively through a medical chart review. A training manual for data identification, abstraction, and entry has been developed and will be reviewed with all data abstractors to ensure consistency across practices. An

experienced medical record abstractor from Moffitt Cancer Center will be designated and trained as the chief abstractor for this project. This individual will train and monitor all the other data abstractors at each affiliate site in a three phase approach. The first phase consists of detailed on-site training. The chief abstractor will review five cases of non-small cell lung cancer from 2011 with each abstractor to ensure accuracy and reliability of data collection. During the second phase, each abstractor will review five additional cases from 2011. The same charts will be reviewed independently by the chief abstractor and assessed for concordance. Additional training will be provided if necessary before practices are approved for project initiation. The third phase will occur after the completion of the initial 15 cases of each disease at each practice; the chief abstractor will review five randomly selected cases of each disease to ensure ongoing quality of data collection and entry.

Data Submission
Data will be managed and entered by the MCC Survey Methods Core [SMC]. Using a prepared Scanform, the abstraction form is transformed into a document that can be read by an optical scanner. The SMC offers this service using Teleform by Verity software, which is a high-accuracy content capture system for automatically processing paper-based forms and document content. Use of scannable forms increases efficiency and can reduce operating costs and errors associated with manual data entry.

Final summaries of the abstraction forms will be compiled by the SMC. The SMC will work with the investigators to ensure a data dictionary and protocol for handling errors and missing data has been established prior to the commencement of scanning. Typically, the SMC staff meets with the investigator, data manager, and statistician to review all instruments for readability to skip patterns and to discuss a plan for handling double scored or missing data. Form completed on online will be automatically compiled into one Access database suitable for exporting into a statistical software package (e.g., SAS) via DBMS Copy. All persons working with the data will be required to sign confidentiality statements. Dr. Pinder-Schenck will be responsible for managing and maintaining the survey database.

Statistical Analysis
Descriptive statistics and graphs will be used to summarize the study variables. Overall and practice-specific adherence rates and the 95% confidence intervals will be calculated for each indicator and each disease, using the exact binomial distribution. Variation in adherence across practices will be evaluated by Pearson's exact test using Monte Carlo estimation of exact p-values. All p-values will be two-sided and declared significant at the 5% level. A prior statistical power evaluation for the sample sizes and multiplicity was not considered given the exploratory nature of analyses designed to examine variation among practices. Therefore, the study is not intended to be powered to detect differences but to serve as pilot data for future large-scale studies.

Stage 2. Report the results of the baseline analysis to the FIQCC sites and develop specific guidelines, educational training tools and practice interventions at a strategic meeting.

Data Reporting
Moffitt-based investigators will prepare a report summarizing the results from stage 1 and comparing each site to each other and to the aggregate data. The rates for practices other than the practice that contributed the data will be presented in masked form to preserve anonymity per agreement with the participating institutions. In anticipation of a strategic meeting for all participating FIQCC sites, individual sites will be encouraged to share results at their tumor board meetings and cancer committee meetings, thus generating discussion about possible solutions for quality improvement.

In addition, Moffitt investigators will prepare a report for presentation and publication describing the development and implementation of this project and summarizing the performance of the participating sites relative to the identified quality indicators. No specific site will be identifiable from the information reported. This report will be presented at a meeting of all FIQCC sites.

Strategic Meeting
Prior to the meeting, individual practice and aggregate data on the molecular testing quality indicators will be shared as described above. Working groups based on disciplines (pathology, medical oncology, thoracic surgery, interventional radiology, pulmonology, oncology nursing, and information technology) will be formed to review national guidelines, discuss performance on quality indicators and to develop discipline-specific interventions to improve adherence to quality indicators. Each working group will be responsible for drafting discipline-specific standard operating procedures and/or procedural checklists. The use of procedural checklists has resulted in improved safety and adherence to standard operating procedures in multiple disciplines.[23, 24] Because of this track record, procedural checklists have been selected as one of the interventions for improving molecular testing practices. In addition, working groups will draft discipline-specific test questions designed to assess practitioner knowledge regarding best practices for use in on-line teaching modules.

At the meeting, a review of the quality indicators and results of the data abstraction from stage 1 will be presented by Dr. Pinder-Schenck. Working groups from each discipline will present proposals for knowledge assessment and practice interventions. Multidisciplinary working groups will be formed at the meeting to address specific areas of need identified by the analysis of the baseline data on adherence to molecular testing quality indicators. These groups will also provide feedback on the discipline-specific tools developed by individual sites and the pre-meeting working groups. Finally, the multidisciplinary working groups will generate a draft of specific practice interventions and teaching tools (to include both web-based and live education) for implementation.

Stage 3. Develop and implement tools and practice interventions at FIQCC sites
Practice interventions and teaching tools proposed at the strategic meeting of participating FIQCC sites will be developed. Dr. Pinder-Schenck will work closely with Ms. Pratt and a research associate (to be hired) to refine the teaching tools proposed at the strategic meeting. These will likely include forms (such as procedural checklists) which can be downloaded from a project website as well as on-line teaching tools. Specific teaching modules will be designed for different disciplines. Additionally, Dr. Pinder-Schenck will work with leaders across different disciplines to design continuing medical education presentations for physicians and oncology nurses. Ms. Pratt and Dr. Pinder-Schenck will design educational materials and presentations for patients aimed at increasing knowledge and awareness of molecular testing, based on feedback from patient advocates. These presentations will be conducted by Dr. Pinder-Schenck and other stakeholders at FIQCC sites and surrounding communities. In addition, a physician, a nurse and a patient advocate from each FIQCC site will be designated for detailed training in the molecular testing toolkit and presentations and will conduct training and troubleshooting at their sites. Given the expertise of the research team, the track record of the FIQCC in successfully executing similar projects and the strong evidence-based practice guidelines and tools to be implemented, successful completion of our project and realization of our goal to improve molecular oncology practices is feasible.

c. Evaluation Design

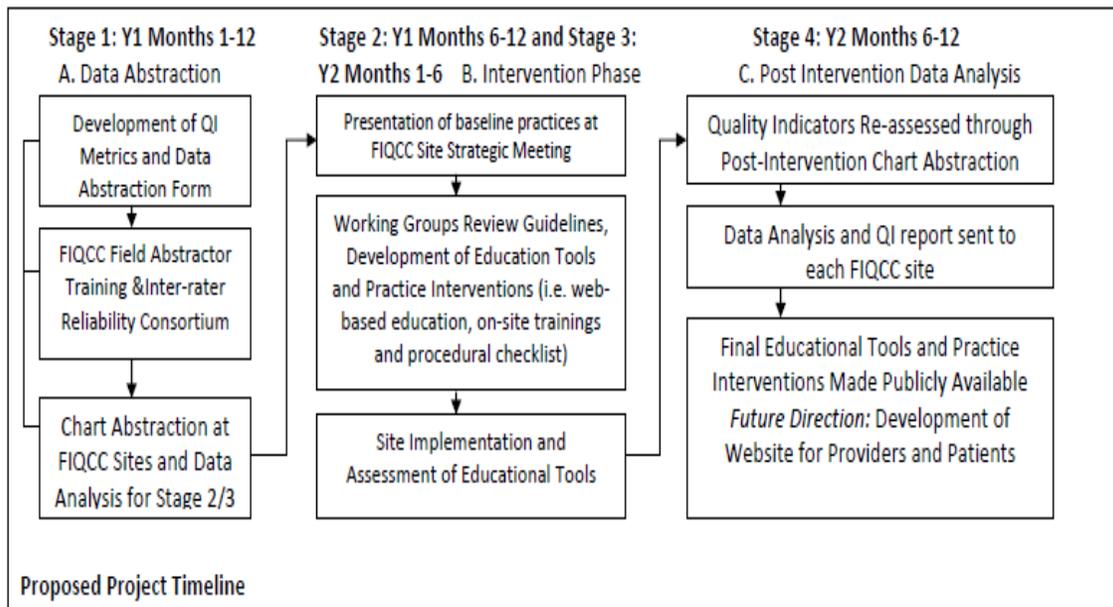**Stage 4. Evaluate and report the impact of tools and interventions**
The process by which we develop our practice interventions and training tools will involve a large number of stakeholders from diverse practices throughout the state of Florida. Built into our project is a plan to resurvey medical records at practices included in stage 1 (baseline survey of molecular testing practices). This will allow us to determine the impact of analyzing and reporting practice patterns (stage 1-2) as well as developing and implementing tools and education to improve practices around molecular testing (stage 3). The practices will serve as their own controls because they will be compared to their baseline (pre-intervention) data. We will analyze medical records from the first half of 2014 utilizing the same inclusion, exclusion criteria and study design, and data reporting described above in stage 1.

Another component of our evaluation of the impact of our interventions will come from data collected from our training tools. Part of our on-line training tools with include case presentations with pre- and post-tests to assess baseline knowledge and to determine the effect of the on-line educational presentation on knowledge of molecular testing practices. We will be able to analyze differences between individuals' pre and post-test performance and will also be able to analyze aggregate differences. At the conclusion of our project, we plan to make our training tools publicly available, which will potentially allow us to analyze the impact of these interventions on a much larger audience in the future.

Statistical Analysis

For the comparison to be performed between the baseline analysis of cases seen in 2012 and cases seen in the first six months of 2014, we seek to determine the direction and magnitude of change on individual performance indicators for individual practices and for all practices combined. The performance rates between the two time periods on individual indicators for all practices combined will be compared using the Fisher's exact test, assuming that the individual patients' charts collected across the two time periods are independent. Further, multivariable logistic regression models will be used to adjust for covariates such as practice site, age, and/or volume. The practice site will be explored and tested in the models as a fixed or random effect. These analyses will be also conducted for individual practices. These analyses will be conducted for exploratory and pilot purposes. Consequently, a prior statistical power evaluation for the sample sizes and multiplicity was not considered.

III. Detailed Workplan and Deliverables Schedule

Stage 1: Y1 Months 1-12 A. Data Abstraction	Stage 2: Y1 Months 6-12 and Stage 3: Y2 Months 1-6 B. Intervention Phase	Stage 4: Y2 Months 6-12 C. Post Intervention Data Analysis
Development of QI Metrics and Data Abstraction Form	Presentation of baseline practices at FIQCC Site Strategic Meeting	Quality Indicators Re-assessed through Post-Intervention Chart Abstraction
FIQCC Field Abstractor Training &Inter-rater Reliability Consortium	Working Groups Review Guidelines, Development of Education Tools and Practice Interventions (i.e. web-based education, on-site trainings and procedural checklist)	Data Analysis and QI report sent to each FIQCC site
Chart Abstraction at FIQCC Sites and Data Analysis for Stage 2/3	Site Implementation and Assessment of Educational Tools	Final Educational Tools and Practice Interventions Made Publicly Available *Future Direction:* Development of Website for Providers and Patients

Proposed Project Timeline

The proposed project will be implemented in four stages over a two year funding period (01/01/2013-12/31/2014). Upon receiving funding announcement, each participating site will submit the project protocol to the institutional review board (IRB) seeking exemption status. If the study is not deemed exempt, each site will obtain IRB approval before entering into Stage 1. In Stage 1 of the proposed project (01/2013 – 06/2013), we will develop a data abstraction form based upon molecular testing quality indicator metrics for lung cancer. The lead site's Survey Core will develop a web-based database. Each Florida Initiative for Quality Cancer Care (FIQCC) site will receive training to conduct the retrospective medical chart review. After completion of abstraction training, each site will begin the retrospective medical chart abstraction to determine baseline

practices and to identify systems and site-specific gaps. Chart abstraction will be completed by 06/2013. Stage 2 and Stage 3 marks the intervention phase of the proposed project (06/2013-06/2014). The results of our baseline analysis will be presented to the FIQCC sites at a strategic meeting to be held at Moffitt Cancer Center in 07/2013. At the strategic meeting, multi-disciplinary stakeholders from each FIQCC site will provide feedback on molecular testing practices and form working groups to develop specific guidelines, educational training tools and practice interventions. These tools will be further refined by the Moffitt team and shared with FIQCC stakeholders for feedback prior to their implementation. Web-based education, tools and procedural checklists developed in Stage 2 will be implemented at each FIQCC sites during Stage 3. In Stage 4 (06/2014-12/2014), we will evaluate and report the impact of tools and interventions by conducting a post-intervention medical chart review. The same study design, data abstraction form and web-based data entry system will be used as for stage 1. A final report will be generated for each site outlining both the baseline and post intervention abstraction results. The educational tools and practice interventions developed in Stage 2 will be made publicly available to outside institutions and a manuscript will be developed.

Deliverable Schedule

	Date	Amount	Project Deliverable	Description of Deliverables
Deliverable 1	01/2013	$115,000	Signed LOA and Site Contracts	Funds include FIQCC contractual site fees, portion of investigator salaries; development of web-based database (Survey Core); site abstractor training
Deliverable 2	07/2013	$93,083	Progress Report Indicating Completion of Stage 1 Data Abstraction and Analysis	Funds include investigator salaries; development of tools web-based educational tools and interventions; strategic meeting fees
Deliverable 3	1/2014	$75,000	Progress Report Indicating Completion of Strategic Meeting and Development of Intervention Tools	Scientific meeting travel; web-based database for post-intervention
Total Requested (Directs and F&A Costs)		**$283,093**		

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