The following template delineates the structure and headings that should be provided in grantee final reports on projects to be submitted to AHRQ as part of the close-out of grant awards. Electronic versions of the final reports will be made available through the AHRQ Web site and the National Technical Information Service. The only acceptable format is Word®. PDF files are **not** acceptable for the Final Progress Report.

Length of Report

4-20 pages maximum, including a Title Page and all components listed below.

Title Page

Include the following:

- **Title of Project**.
  - Understanding and Promoting Best Practice in Molecular Testing for NSCLC Patients in Florida
- **Principal Investigator and Team Members.**
  - Alberto Chiappori, MD
  - Gwendolyn P. Quinn, PhD
  - Ji-Hyun Lee, DrPH
  - Christie Pratt, M.A., DHsc
- **Organization.**
  - H. Lee Moffitt Cancer Center
- **Inclusive Dates of Project**.
- **Federal Project Officer.**
- **Acknowledgment of Agency Support.**
- **Grant Award Number.**

Report Components

Include the following six components using these headings:

1. **Structured Abstract** (Select for Elements).
   See below

2. **Purpose** (Objectives of Study).
   - Evaluate current practices and barriers to lung cancer molecular testing in the state of Florida; and
   - Develop sustainable and comprehensive practices through the Moffitt Oncology Network (MON) to ensure access to molecular testing and appropriate targeted therapy for patients with advanced lung cancer.

3. **Scope** (Background, Context, Settings, Participants, Incidence, Prevalence).
   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, we propose this study.

4. **Methods** (Study Design, Data Sources/Collection, Interventions, Measures, Limitations).
   This project will assess and improve molecular testing for lung cancer patients on a systems level. We will utilize the infrastructure of the MON 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 4 stages, described below in detail:

   Stage 1. Medical record review at selected MON affiliate 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 2013. Random samples of 50 patients will be selected at each MON 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 2012 with each abstractor to ensure accuracy and reliability of data collection. During the second phase, each abstractor will review five additional cases from 2012. 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. Chiappori 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.

<u>Stage 2.</u> Report the results of the baseline analysis to the selected MON affiliate 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 (Web Teleconference) for all selected MON affiliate 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 (Web Teleconference) of all selected MON affiliate sites.

Strategic (Web Teleconference) 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 (Web Teleconference), a review of the quality indicators and results of the data abstraction from stage 1 will be presented by Dr. Chiappori. Working groups from each discipline will present proposals for knowledge assessment and practice interventions. Multidisciplinary working groups will be formed 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. 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.

<u>Stage 3.</u> Develop and implement tools and practice interventions at selected MON affiliated sites

Practice interventions and teaching tools proposed at the strategic (Web Teleconference) meeting of participating MON affiliated sites will be developed. Dr. Chiappori 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. Chiappori will work with leaders across different disciplines to design continuing medical education presentations for physicians and oncology nurses. Ms. Pratt and Dr. Chiappori 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. Chiappori and other stakeholders at selected MON affiliated sites and surrounding communities. In addition, a physician, a nurse and a patient advocate from each MON affiliated 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 Moffitt Thoracic Oncology department in successfully executing investigational 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.

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 second half of 2015 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 2013 and cases seen in the last six months of 2015, 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.

5. **Results** (Principal Findings, Outcomes, Discussion, Conclusions, Significance, Implications).

I became the PI for this study in April 2014, due to Dr Mary Pinder-Schenk's (original PI) departure from the Moffitt Cancer Center and after more than 1 year delay due to administrative reasons that have been addressed previously.

Project Timeline

From the beginning, the focus became the activation of the trial and so, once the protocol was modified and adapted to the to the required Moffitt Cancer Center template, the protocol was submiited for SRC review and approval. Simultaneously, we also begun working in the data abstraction form that would have to be submitted for approval to the IRB with the protocol, once SRC approval was obtained.
A data abstraction training manual with a data abstraction form was created and reviewed by the PI in June 2014. The final training manual and abstraction form were approved and uploaded for SRC

approval in August 2014. In the interim a data dictionary was built to co-inside with the training manual and abstraction form. this was accomplished in coordination and collaboration with the …… so that the data could be collected electronically, without the need of hard copies, from the different participating sites in real time.

The protocol was submitted to the SRC on August 15, 2014 we received notice of approvability on September 8, 2014 with a required response for SRC concerns. We responded to their concerns with a letter and the data abstraction form on September 12, 2014 which was subsequently re-submitted for review and SRC approval. After the SRC reviewed the re-submission we were given a still missing status as of September 26, 2014. Alberto Chiappori, MD reworked the protocol, updated the missing information and the resubmission happened on September 29, 2014 with approval status the same day.

We then sent our SRC approved protocol to Liberty IRB, we were given an expedited review status and were approved on October 6, 2014 and activated on October 22, 2014 (including data abstraction form). Once IRB approved we submitted a data request to our internal information shared services department on October 28, 2014 to seek the appropriate subject information for the abstraction. On January 6, 2015 we contacted our survey core department to help us create an online version of the data abstraction form. After several meetings and testing of the online version we had a final clean version on July 31, 2015.

Simulatneously, the selection process for site participation was also initiated in June 2014. Originally, the plan had been to conduct the trial with the participation and cooperation from the FIQCC. However, given the prolonged administrative delay in trial activation, by this time, the work and funding for the FIQCC had been completed and thus not anymore able to collaborate. Alternatively, through the Moffitt Oncology Network (MON), we were able to identify and select 4 different Florida member sites for participation; Watson Clinic in Lakeland FL, Ocala Oncology in Ocala FL, Space Coast Cancer Center in Titusville FL and Martin Memorial Hospital in Stuart FL.

With obtention of IRB approval at the Moffitt Cancer Center, in October 2014, the process moved forward with activation of the accepting sites. On January 22, 2015 we reached out to our final four MON approved sites that were interested in participating in this data abstraction project with instructions for them to obtain their own IRB approval, subsequently we attached our IRB approval for their final determination. Ocala Oncology contacted us in February of 2015 with their approval from the IRB. Unfortunately, we were contacted in April 2015 by the other 3 participants for final review: one rescinded due to the closing of their research department and 2 rescinded due to the lack of eligible subjects for the abstraction.

At the Moffitt Cancer Center, during this period of time, we begun first with the “testing of the Data abstraction form”. This consisted in the collection of 5 sample charts to test proof the utility of the form. Subsequently, we initiated collection of the Moffitt samples. This list was generated and reported to us on November 26, 2014 with a 198 patients listed. This list still had to be narrowed down to fit into the criteria of our protocol. We used several of the patients on this list as a test for our data abstraction form and found that the form needed to be updated and a final draft was completed on December 1,

2014. The list was re-worked and narrowed down by the eligibility criteria to 99 patients; this was finished on May 22, 2015.

In June 2015 we spoke with Ocala Oncology they had 600 records that needed to be narrowed down to comply with our eligibility criteria, they asked for a stipend to help offset the startup costs prior to training. We received an invoice from Ocala Oncology on June 18, 2015 requesting said stipend and a purchase order was submitted with payment mailed on July 23, 2015.

We began our training with Ocala Oncology July 29, 2015 and continued the training until July 31 2015. After the initial training it was determined that Ocala Oncology would have a final count of 10 eligible subjects for the abstraction.

Patient Characteristics Table

		Moffitt n (%)	Ocala n (%)	Total n (%)
		50	10	60
Insurance status				
	Private	15	3	18 (30.0)
	Medicare	33	7	40 (66.7)
	Charity	2	0	2 (3.3)
Age				
	> 50	3	0	3 (5.0)
	51-70	30	6	36 (60.0)
	> 70	17	4	21 (35.0)
Sex				
	Male	28	7	35 (58.3)
	Female	22	3	25 (41.7)
Race				
	Asian	2	0	2 (3.3)
	Native Am./Hawaiian	1	0	1 (1.7)
	Black	2	1	3 (5.0)
	White	44	8	52 (86.7)
	Hispanic	1	0	1 (1.7)
	NR	0	1	1 (1.7)
Marital Status				
	Single	8	0	8 (13.3)
	Married	39	8	47 (78.3)
	Widowed	3	0	3 (5.0)
	Divorced	0	1	1 (1.7)
	UKN	0	1	1 (1.7)
Smoking history				
	Current	12	1	13 (22.0)
	Former	31	8	39 (65.0)
	Never	7	1	8 (13.0)
Smoking duration (n)		41	5	
	Median (range)	37 (2-65)	43 (20-63)	

	Mean - average	36.7	45.2	
Smoking amount – average (ppy)				
	Median (range)	44 (1-164)	81.5 (30-126)	
	Mean - average	47.1	82.3	
Histology				
	Adenocarcinoma	36	5	41 (68.0)
	Squamous cell	12	3	15 (25.0)
	Large cell	0	0	0 (0.0)
	NOS	0	1	1 (2.0)
	other	2	1	3 (5.0)
Stage at Dx				
	Stage IV	47	10	57
	UNK	3	0	3
ECOG PS				
	0-1	42	0	42
	≥ 2	8	0	8
	NR	0	10	10
First Bx. Molecular analysis (MA) – ordered (n)		32	3	35 (38.0)
	Time to MA order from Bx – median (days)	15.5 (0-49)	7 (0-14)	16
	Time to MA results from Bx – median (days)	35 (8-61)	10 (4-16)	32
	Time to MA results from order – median (days)	14.5 (3-34)	3 (2-14)	16
Second Bx. – ordered (n)		9	2	11
Second Bx. MA – ordered (n)		7	2	9 (82.0)
	Time to MA order from Bx – median (days)	0 (0-27)	18 (0-36)	
	Time to MA results from Bx – median (days)	12 (0-33)	32.5 (27-38)	
EGFR				
	No. tested	25	3	28
	No. positive	5	0	5
	No. on TKI (erlotinib)	5	0	5
	Survival EGFR TKI – average (days)	42,808,735,756,437		
ALK				
	No. tested	24	3	27
	No. positive	1	0	1
	No. on TKI (crizotinib)	1	0	1
	Survival ALK TKI – average (days)			
Overall Survival: (95% CI):		295;(201,387)	129;(81,387)	

6. **List of Publications and Products** (Bibliography of Published Works and Electronic Resources from Study—UseAHRQ Citation Style for Reference Lists).

Structured Abstract—Five Elements:

Structured Abstracts can have a maximum of 250 words.

Purpose:

Improving care for lung cancer patients in Florida and building a solid foundation for molecular testing in the future through the Moffitt Oncology Network.

Scope:

Approximately 50% of adenocarcinomas will harbor an actionable mutation. 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 for performing, reporting and utilizing molecular testing in these patients.

Methods:

This project will assess and improve molecular testing for lung cancer patients on a systems level. We will utilize the infrastructure of the MON 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 4 stages.

Results:

- Similar patient distribution in terms of insurance status, age, sex, marital status and stage by cohorts
- More race diversity, more singles, and more adenocarcinomas in the MCC cohort
- Ocala cohort included heavier smokers and more former smokers
- Molecular analysis (MA) was more frequently requested in the MCC cohort with first biopsy
- MA frequency similar with second biopsy, but ordered faster at MCC

Conclusions:

- Initial administrative delays precluded proper conduction of study
- Only one MON site was able to participate
- Small sample size precludes arriving to valid conclusions
- Observations suggest areas where education and collaboration may be benefitial for improvement

Key Words: lung cancer, MCC, Ocala, molecular analysis