

# **NCCN/Lilly Request for Proposals (RFP) to Optimize Biomarker Driven Therapy in Lung and Thyroid Cancers**

## **I. Introduction**

National Comprehensive Cancer Network® (NCCN) and Eli Lilly and Company (Lilly) are collaborating to offer a new funding opportunity seeking proposals to improve patient care and outcomes in lung and thyroid cancers. Multiple factors contribute to the complexity of treating these diseases, including stage and histology, personalization of systemic therapy based on molecular profiles, patient factors, and therapeutic landscape.

The intent of this RFP is to encourage NCCN Member Institutions to submit proposals describing concepts and ideas for developing, implementing and evaluating healthcare provider performance and/or healthcare quality improvement initiatives to improve patient care and outcomes in relation to molecular profiling and targeted therapies for lung and thyroid cancers. Investigations aimed at improving quality of lung and thyroid cancer care at all time points along the clinical care continuum will be considered. Special consideration will be given to projects that are developed in collaboration with health system-based network practices or community-based practices. This RFP aims to improve translation of best practices and current data to enhance the quality of cancer care in lung and thyroid cancers.

NCCN is a not-for-profit alliance of 31 leading cancer centers devoted to patient care, research, and education. NCCN is dedicated to improving and facilitating quality, effective, efficient, and accessible cancer care so patients can live better lives. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops resources that present valuable information to the numerous stakeholders in the health care delivery system. By defining and advancing high-quality cancer care, NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers around the world.

This Request for Proposals (RFP) is issued by NCCN and is available only to applicants from NCCN Member Institutions. A review committee, led by NCCN, will make decisions on which proposals will receive funding. Funding will be provided by NCCN through support from Lilly.

## **II. Background**

It is well established that predictive biomarker testing on tumor-derived tissue or circulating DNA (ctDNA) plays an important role in the treatment decision-making for both metastatic non-small cell lung cancer (NSCLC) as well as metastatic thyroid cancers. Such an approach has commonly been termed either personalized medicine or precision medicine. There are now multiple FDA-approved targeted therapies available to treat patients with actionable mutations associated with favorable response rates, progression free survival, side effect profiles, and/or overall survival advantages compared to non-biomarker selected treatment options. However, rates of testing in patients vary widely, and recent data suggest a significant proportion of patients may never receive the appropriate biomarker testing and appropriate treatment options. Several barriers exist regarding the optimal implementation of personalized or precision medicine strategies (strategies which employ such predictive biomarkers for treatment decision-making), including the range of assays available, access to appropriate tissue, assay

turnaround time, assay reimbursement, coordination of multiple different stakeholders and appropriate interpretation of the results.

#### NSCLC:

The frequency of actionable genetic abnormalities in NSCLC vary by country, histology, sex and smoking status. Estimates of the rate of actionable alterations for NSCLC in the US range between 20-45%. In a recent American Society of Clinical Oncology (ASCO) presentation in June 2021, less than 50% of patients with metastatic NSCLC were tested for all five of the most common actionable (at the time of the study) biomarkers.<sup>1</sup> Whether such data should be taken at face value or whether the proportion of patients being under-explored for molecular markers should be quantified in a different manner remains under investigation. For example, given that at diagnosis most of the predictive biomarkers are considered mutually exclusive, in theory if a positive result is found, the relevance of testing other biomarkers is less well established. As such, the true number being under-investigated may be better defined as those *without a positive biomarker diagnosis* who did not receive all relevant testing. The definition of ‘relevant testing’ also has to be considered a concept in flux. There are now currently eight different oncogene-related biomarkers with approved FDA-indicated therapies in metastatic NSCLC (see Table 1 for a list). In addition, although these genetic markers are considered mutually exclusive at diagnosis, PD-L1 tumor proportion score (TPS) should be considered a 9<sup>th</sup> predictive biomarker, and is recommended to be tested in all patients. However, when a high PDL-1 score overlaps with a driver oncogene the oncogene is almost always prioritized in the initial decision-making. Additional genetic biomarkers are listed in the NCCN Guidelines including HER2 mutations and High MET amplification.

**Table 1.** Actionable biomarkers in NSCLC with an FDA approved therapy as of July 2021

EGFR mutations (EXON del19, EXON 20 insertion, EXON 21/L858R)
KRAS <sup>G12C</sup> mutation
ALK gene rearrangement
ROS1 gene rearrangement
BRAF V600E mutation
RET gene rearrangements
MET Exon 14 Skipping mutation
NTRK gene rearrangements
PD-L1 expression

Genetic biomarkers in the above list may be detectable from analyses conducted on tumor tissue or tumor-derived circulating DNA, relevant cytogenetic or immunohistochemical assays. Each methodology has its own advantages and disadvantages in terms of cost, turnaround time, and its positive and negative predictive values. For detection of targetable biomarkers in NSCLC, combining both tissue and blood testing has yielded the highest percentage of positive findings.<sup>2,3</sup> However, such analyses need to clearly define what a ‘positive’ finding means differentiating true driver oncogene results from genetic changes which may not necessarily be either tumor-derived or relevant for treatment decision-making.

The complexity and procedural flow of obtaining precision medicine tests may be one major barrier to its wider implementation. Biomarker testing in NSCLC requires collaboration between multiple stakeholders, potentially including pulmonology, interventional radiology, surgery, medical oncology and pathology. Testing needs to be accurately and appropriately ordered and the results retrieved and appropriately integrated into the patients records and appropriately acted upon. The specific testing requested may need to balance competing demands of single versus multiple gene testing, or other

multiplex testing, with regard to reimbursement, tissue requirement, turnaround time, and available resources. When testing has not occurred or when a positive result has not been obtained, actions to determine if additional tissue or blood sampling or repeat or different testing is required may neither be routine, nor incentivized.

### Thyroid Cancers:

Most differentiated thyroid cancers (DTC) may be managed with surgery, with or without radioactive iodine. In the setting of more advanced disease, precision medicine has an important role in those patients who have radioiodine (RAI)-refractory locoregionally recurrent unresectable and/or metastatic disease no longer amenable to these approaches. Around 60% of DTCs have actionable mutations or gene rearrangements.<sup>4</sup> Papillary thyroid cancer (PTC) is the most common type of metastatic thyroid cancer. Approximately 10 to 15% of PTCs are not cured with standard therapy. Currently, both *RET* and *NTRK* gene rearrangements can give rise to PTC and have FDA-approved medications for advanced PTC once these biomarkers are identified. Poorly differentiated and anaplastic thyroid cancers that can arise out of a more well-differentiated PTC can also harbor these driver alterations. Moreover, a majority of medullary thyroid cancers (MTC) harbor activating *RET* mutations. 20-25% of MTCs are seen in patients with familial MEN 2A or B syndromes; essentially all of these patients harbor germline *RET* mutations. Of the 75% of MTCs that arise sporadically, around 50-60% harbor somatic *RET* mutations. Thus, a majority of patients with MTC have *RET*-driven disease for which *RET*-inhibitor therapy is also FDA approved.<sup>5</sup>

See Table 2 for a comprehensive list of actionable biomarkers across the spectrum of thyroid cancers.

Currently the NCCN recommends testing thyroid cancer for *RET* and *NTRK* gene rearrangements, *BRAF* mutations, and Tumor Mutational Burden (TMB) for all PTC, anaplastic thyroid cancer (ATC), follicular thyroid cancer (FTC) and Hürthle Cell Thyroid cancers. For MTC, testing for somatic mutations of *RET* is recommended, as well as germline mutation testing, for *RET* mutations.

**Table 2.** Actionable biomarkers with FDA approved therapies in metastatic thyroid cancer as of July 2021

	<i>RET</i> Indications	<i>BRAF</i> Indications	<i>NTRK</i> Indications
Differentiated Thyroid Cancer*	X		X
Anaplastic Thyroid Cancer	X	X	X
Medullary Thyroid Cancer	X		

\*Includes PTC, FTC and Hürthle Cell Thyroid cancers

There is limited data on the routine extent of biomarker testing in thyroid cancer. In MTC, there is a well-established role for germline testing, but not all patients complete this testing. Barriers to testing included older age and shorter survival.<sup>6</sup> Other potential barriers may include limited understanding about the nuances and differences in germline and somatic testing. While some thyroid cancers have an indolent phenotype, anaplastic thyroid cancers tend to be aggressive with rapid growth which shortens the acceptable interval for return of molecular study results. Many of the same barriers to testing in thyroid cancer are similar to NSCLC. Due to a lack of familiarity with these rare tumors, relative to NSCLC, there may also be an under-appreciation of molecular testing and treatment options in routine clinical practice.

There are several commercial tests available (e.g. Afirma and Thyroseq) for the diagnostic workup of thyroid nodules that may identify actionable biomarkers that may be used in the future when systemic therapy is necessary. However, they do not all utilize the same methods and are not interchangeable, causing further confusion in this testing space. Lastly, optimal timing of precision medicine testing during the disease course is not well described within the literature and many patients may miss a window of opportunity for treatment or clinical trials for their druggable mutation or gene rearrangement.

#### **Goals:**

This RFP aims to explore the barriers to biomarker testing from tissue acquisition to treatment initiation which may result in missed or delayed treatment opportunities leading to sub-optimal treatment outcomes. Adherence to the NCCN guidelines for testing in NSCLC and advanced thyroid cancers promotes a standardized approach to biomarker testing across all practice settings in these diseases.

Projects should propose novel ideas to overcoming barriers to biomarker testing in NSCLC and metastatic thyroid cancer. Additionally, proposals that include novel ways to educate patients to be better advocates for themselves through self-empowerment regarding the importance of biomarker-based treatment initiation are encouraged. Ideal solutions would be able to be disseminated and scaled to encompass both academic and community-based practices throughout the United States.

### **III. Scope**

The overall aim of this RFP is to develop innovative healthcare provider performance and/or quality improvement initiatives to improve patient care and outcomes in NSCLC and thyroid cancer. It is hoped that results from projects funded can be quickly disseminated to other practices and settings to rapidly improve delivery of cancer care. The goal is to provide funding to projects that, ultimately, are aimed at helping healthcare professionals deliver the optimal guideline-adherent treatment to each patient at the appropriate time.

This RFP is open to investigators from NCCN Member Institutions. The principle investigator (PI) must be from a NCCN Member Institution. Collaboration between NCCN Member Institutions and other institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the combined strengths of investigators. Special consideration will be given to projects that are developed in collaboration with health system-based network practices or community-based practices. Funding for co-investigators will be routed through the NCCN Member Institution. Proposal submissions from Junior Faculty are encouraged. Trainees may participate as a sub-investigator under the appropriate mentorship from a PI from a NCCN Member Institution.

**Only projects specific to the care of NSCLC and thyroid cancer patients will be considered for funding.**

**The areas of emphasis identified for this RFP include the following:**

1. Identification of, and interventions to address barriers to optimal precision medicine (e.g. adherence to NCCN Guidelines) as it applies to testing methodologies, timing of testing, causes of delay, actions based on testing, and initiation of appropriate treatment which may include:
  - a. Improvement of tissue acquisition and conservation of tissue;
  - b. Empowerment and education of patients and their families;
  - c. Process improvements for biomarker testing and reporting; and

- d. Developing education tools for clinical practices describing biomarker testing, checklists, incentives, and engagement.
2. Decision support in thyroid cancer regarding the use of biomarker-directed versus non-directed therapy.
3. Evaluation of health care provider performance or quality of care resulting in improved outcomes for biomarker-positive NSCLC or metastatic thyroid cancer.
4. Projects that can be scaled out to cancer network practices and community settings.
5. Utilization of health technology and innovation to improve biomarker testing in NSCLC and Thyroid cancer.

**Areas of particular interest include:**

1. Projects that include community and network partnerships.
2. Projects that explore and define new barriers and offer solutions.
3. Projects that offer solutions to barriers related to disparities in access or in otherwise underserved communities.

**All funded proposals must:**

1. Promote evidence-based care;
2. Be sustainable after the award funding is complete;
3. Collect data and report outcomes;
4. Have a goal to enhance clinical outcomes, patient satisfaction, or provider satisfaction;
5. Be flexible enough to address patient variability; and
6. Promote administrative and system efficiency.

In addition, proposals that are scalable, reproducible, and quickly implementable, with tangible outcomes, are preferred. Ideally, proposed projects will offer a roadmap with a short runway to launch and demonstrate the ability to maintain timelines for deliverables (within two years).

**Specific exclusions from this RFP include:**

1. Therapeutic clinical trials (unless the quality aspects are affected in a pre-existing therapeutic clinical trial).
2. Educational projects without deliverable outcomes.
3. Projects that only define problems that have already been identified.
4. Non-NCCN Member Institution applicants.
  - a. Non-NCCN Member Institutions may participate in an NCCN Member Institution-led collaboration.

**IV. Requirements**

<b>Date RFP Issued:</b>	August 3, 2021
<b>Clinical Area:</b>	Lung and Thyroid Cancer
<b>Target Audience:</b>	Members of the health care team and administrators involved in the care of lung and thyroid cancer patients at NCCN Member Institutions and associated community practices.  Specific populations: community-based practices, patient populations with disparities and underserved communities.

<b>Applicant Eligibility Criteria:</b>	NCCN Member Institutions
<b>Expected Approximate Monetary Range of Applications:</b>	Total funding available is \$1.2 million. It is expected that 4-6 projects will be funded.  Budgets over \$300,000 will be considered in exceptional cases with sufficient justification.
<b>Estimated Key Dates:</b>	Full Proposal Deadline: <b>September 28, 2021</b> Please note the deadline is 5:00 pm Eastern Time.  Anticipated Full Proposal Notification Date: <b>November 2021</b>  Period of Performance: <b>Two years</b>
<b>How to Submit:</b>	Please email your Proposal submission to <a href="mailto:NCCNLillyQualityProject@nccn.org">NCCNLillyQualityProject@nccn.org</a>  <b>IMPORTANT:</b> Be advised that proposals submitted to the wrong email address or after the due date will not be reviewed by the committee.
<b>Selection Criteria:</b>	Applications will be evaluated on the basis of: <ul style="list-style-type: none"> <li>• Knowledge of and experience with the area;</li> <li>• Capability of carrying out the work within a two-year timeframe;</li> <li>• Collaboration if appropriate;</li> <li>• Scalability and sustainability;</li> <li>• Potential effect and expected outcomes of the project; and</li> <li>• Dissemination strategies.</li> </ul>
<b>Questions:</b>	If you have questions regarding this RFP, please direct them in writing to Nicole Zion at <a href="mailto:zion@nccn.org">zion@nccn.org</a> with the subject line "2021 Lilly Quality Project".
<b>Mechanism by which Applicants will be Notified:</b>	All applicants will be notified via email by the anticipated dates noted above.  Applicants may be asked for additional clarification if needed.

## **V. Proposal Submission Guidance**

In order to respond to the RFP, investigators must submit a proposal to NCCN in the format delineated below, which will be evaluated by the NCCN Scientific Review Committee (SRC).

Proposals must be single-spaced, using Calibri 12-point font and 1-inch margins. Note that the main section (section C, below) of the proposal has a 10-page limit and the organization detail (section E, below) has a 2-page limit. There is no reason to submit the organization detail (section E) as a separate document from the main section (section C) of the proposal. All proposals must follow the outline detailed below.

Proposal requirements will include the following sections:

- A. Cover Page (do not exceed 1 page):
  1. Title: Please include the project title, and main collaborators.
  2. Abstract: Please include an abstract summary of your proposal including the overall goal, target population, methods and assessment. Please limit this to 250 words.
- B. Table of Contents (no page limit)
- C. Main Section of the proposal (not to exceed 10 pages):
  1. Overall Goal & Objectives: Describe the overall goal for this project. Describe how this goal aligns with the focus of the RFP, the goals of the applicant organizations and the proposed project. List the key objectives and how they are intended to address the established need for this project.
  2. Current Assessment of need in target area:
    - a. Describe the need for this project in your target area. Only include information that impacts your specific project, linking regional or local needs to those identified on the national basis if appropriate. Describe the need for your project in terms of “what is” versus “what should be”.
    - b. Please include quantitative baseline data summary, initial metrics (e.g., quality measures), or project starting point (please cite data on gap analyses or relevant patient-level data that describes the problem) in your target area. Describe the source and method used to collect the data. Describe how the data was analyzed to determine that a gap existed.
  3. Target Audience: Describe the primary audience(s) targeted for this project.
    - a. Describe the level of commitment from the potential participants including your plan for recruitment as necessary.
    - b. Demonstrate the scope of your target audience has a potential to impact the goal established in this proposal.
    - c. Describe who will directly benefit from the project outcomes. Include in this description whom, beyond the primary target, would potentially benefit from the project in terms of this being a model for others to replicate or expand.
  4. Project Design and Methods: Describe your project design and methods.
    - a. Include a description of the overall strategy, methodology and analysis linking them to the goal of the project.
    - b. Describe the way the project planned addresses the established need and produces the desired results.
    - c. Indicate how you will determine if the target audience was fully engaged in the project.
    - d. Include a description of the measures you have taken to assure that this project idea is original and does not duplicate other projects or materials already developed.
    - e. If appropriate, show how this project builds upon existing work, pilot projects, or ongoing projects developed either by your institution or other institutions related to this project.
    - f. If your project includes the development of tools, note whether they be available publicly at no cost.
  5. Evaluation Design:
    - a. In terms of the metrics used to assess the need for this project, describe how you will determine if the practice gap was addressed for the target group.

- Identify the sources of data that you anticipate using to make the determination.
  - Describe how you expect to collect and analyze the data.
  - Describe how you will determine if the results evaluated are directly related to the intervention described in this proposal.
- b. Quantify the amount of change expected from this project in terms of your target audience. (e.g., a 10% increase over baseline or a decrease in utilization from baseline between 20-40%)
  - c. Describe how you plan for the project outcomes to be broadly disseminated.
6. Detailed Workplan and Deliverables Schedule: Include a narrative (which counts toward the 10-page limit) describing the workplan and outlining how the project will be implemented over the 2-year period. Using a table format (no page limit), list the deliverables and a schedule for completion of each deliverable.

D. References (no page limit)

E. Organizational Detail (not to exceed 2 pages):

1. Organizational Capability: Describe the attributes of the institution(s)/organization(s)/association(s) that will support and facilitate the execution of the project.
2. Leadership and Staff Capacity: Include the name of the person(s) responsible for this project (PI/ project lead (PL) and/or project manager). The project manager, whether a current staff member or someone to be hired, is essential to the work outlined in your proposal. Demonstrate the PI/PL and project manager's availability, commitment, and capability to plan, implement, and evaluate the proposed project; describe how the project manager will oversee the project activities, including ensuring that tasks are accomplished as planned.
  - a. List other key staff members proposed on the project (e.g., healthcare provider champion, medical advisor, statisticians, IT lead, mentors, etc.), if relevant, including their roles and expertise. Please list out key staff for each institution/organization/association the specific role that they will undertake to meet the goals of this project.
  - b. When listing staff, please include staff first name, last name, professional credentials, and country of residence.

F. Detailed Budget (Refer to/Complete Budget Template; no page limit for the Excel file or the narrative):

1. Upload a detailed budget, using the Excel template provided. Applicants are expected to customize the budget for their proposal, adding additional details and deliverables as appropriate.
2. Provide a written narrative that contains a detailed explanation of each cost element proposed. Budget narratives should include a justification for all personnel, indicating the percentage of time allocated to the project. The budget should demonstrate appropriate and reasonable costs for project expenses.
  - a. Institutional overhead and indirect costs may be included within the funding request. (25% maximum)
  - b. The inclusion of these costs cannot cause the amount requested to exceed the budget limit set forth in the RFP.

G. Staff Biosketches (no page limit): Applicants must provide brief Biosketches of all individuals listed in section E in an appendix. NIH Biosketches are an acceptable format, but not required.



H. Letter(s) of Commitment (no page limit):

Letter(s) must be provided from all organizations listed in section E documenting their support and commitment to the project. Letters should be issued from an institutional authority or authorities and collaborators guaranteeing access, resources and personnel (as the case may be) for proposed project. If the QI initiative requires the use of a smart technology, or application to be built, a letter of commitment from that platform/builder must be included.

Submission: Proposals should be submitted via email to [NCCNLillyQualityProject@nccn.org](mailto:NCCNLillyQualityProject@nccn.org). All submissions are due by **September 28, 2021** at 5:00 pm Eastern Time.

Please adhere to the page limits listed for each section. Tables and Figures should be included in the main section of your proposal and do count to the page count. Only sample forms or other full-page documents can be included as an appendix.

All required sections (aside from the budget) should be combined in one document (MS Word or Adobe PDF). There is no need to submit the organization detail or references in a document separate from the main section of the full proposal. Budgets should be submitted in a separate excel file.

#### **VIII. Terms and Conditions**

This RFP does not provide permission and license for the use (including the creation of derivative products) of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for commercial use. Funding recipients will need to maintain a separate end-user or other license agreement directly with NCCN for use of the NCCN Guidelines.

#### **IV. References**

1. Robert, NJ et al. 2021 ASCO oral presentation
2. Leighl NB, et al. Clin Cancer Res. 2019; 25(15):4691-4700
3. Aggarwal C. et al. JAMA Oncol. 2019;5(2):173-180. doi:10.1001/jamaoncol.2018.4305
4. Zehir, *Nature Med*, 2017
5. Ciampi, et al. *iScience*, 2019
6. *Clinical epidemiology* vol. 11 93-99. 10 Jan. 2019