**Announcement to NCTN Network Groups**

**National Cancer Institute (NCI) Clinical Trial Sequencing Project (CTSP):**

**Genomic Characterization of Biospecimens Collected from NCI-Sponsored Trials of the National Clinical Trials Network (NCTN)**

**Key Dates**

**Release Date: March 12, 2015**

**Receipt Dates for Proposals: May 15, 2015 and September 30, 2015**

It is anticipated that this Announcement will be reissued in subsequent years.

**I. Purpose**

The National Cancer Institute’s (NCI’s) Center for Cancer Genomics (CCG) and Division of Cancer Treatment and Diagnosis (DCTD) wish to promote the use of genomics to elucidate the molecular basis of response and resistance to therapies studied in NCI-sponsored clinical trials of the National Clinical Trials Network (NCTN).

**II. Overview and Summary**

NCI CCG and NCI DCTD invite funded NCTN Network Groups (NCTN Operations Centers in conjunction with the relevant group of NCTN investigators) to submit proposals requesting genomic characterization by NCI (or NCI-sponsored laboratories) of biospecimens collected from NCI-sponsored NCTN clinical trials in which clinical data will be mature and available within 6 months of proposal selection. Successful proposals will be those that are hypothesis-driven and propose studies where genomics could answer a key clinical question.

NCI will utilize whole genome sequencing and/or whole exome sequencing in conjunction with transcriptome sequencing to try to identify recurrent genetic alterations (mutations, deletions, amplifications, rearrangements) and/or gene expression signatures that would be important to the hypothesis(es) submitted by the investigators. The samples will be processed and submitted for genomic characterization using pipelines and procedures established within The Cancer Genome Analysis (TCGA) project.

Data analysis will be performed as a collaboration between the NCTN Network Group and its investigators submitting the proposal and the investigators at the NCI-sponsored Genomic Data Analysis Center (GDAC) who characterize the samples. The NCTN Network Group will be responsible for providing the clinical data needed for the proposal to the Open Clinica system maintained by NCI CCG’s Biospecimen Core Resource (BCR) at Nationwide Children’s Hospital in Columbus, Ohio, as outlined in Section VIII. The project team (Network Group/investigators and GDAC) will analyze the data together. Additionally, clinical and genomic data related to the analyses will also need to be registered by NCI and will be made available to qualified researchers via a controlled-access database (e.g., dbGaP) upon publication of the primary analysis described in the study proposal.

**III. Evaluation Process**

Proposals will be reviewed by DCTD’s Cancer Therapy Evaluation Program (CTEP) for scientific merit, appropriateness of the proposed specimens, and appropriateness of consent.

Scientifically meritorious proposals that are recommended by CTEP will be presented by NCI Program Staff to the Clinical and Translational Research Operations Committee (CTROC) for prioritization and approval at its meetings, which are held twice a month. CTROC makes final funding recommendations. The Clinical Trials and Translational Research Advisory Committee (CTAC) periodically reviews the approved funding portfolio, providing strategic oversight and advice.

Proposing NCTN Network Groups should expect to receive a decision on their proposal within two to three months of proposal submission.

**Criteria for Review of Proposals**

Prioritization and evaluation of proposals will include the following considerations:

* The proposed study is hypothesis-driven with a detailed statistical plan
* Genomics could answer a key clinical question(s)
* The study would be able to address its hypothesis(es) with the available biospecimens (e.g., tissue, blood, extracted DNA/RNA)
* Studies of ~500 cases that address a clinical question are optimum, but other sample sizes will be considered based on what is feasible within the total funding available within NCI for the genomic characterization associated with this Announcement.
* Availability of biospecimens (amount) and availability of matched normal tissue/blood from patients who submitted tumor specimens
* Appropriate consents are in place for use of the specimen for this purpose
* Reviewers will also look across proposed studies, to ensure an appropriate mix of studies is approved (e.g., mix of disease areas)

It is not intended that any priority or particular level of merit is assigned to one criterion over another, but rather the proposals will be evaluated based on the totality of the information provided.

**IV. Mechanism of Support**

NCI will fund the genomic characterization. If needed, additional funding can also be requested to cover costs **not** already covered by the NCTN Network Group’s tumor banking grant for locating, assessing, preparing, and shipping the specimens to NCI. Network Groups seeking additional funding for these types of costs should provide a budget with appropriate justification in their proposals.

This NCI Clinical Trial Sequencing Project (CTSP) will be managed through CTEP in collaboration with CCG. For this Announcement, the number of anticipated proposals selected is contingent upon the availability of CCG funds for the characterization and the number of meritorious proposals submitted. Applicants may submit more than one proposal, provided they are scientifically distinct.

**V. Requirements and Definitions**

**A. Eligible proposals**

* Proposals must be submitted by an NCI-funded NCTN Network Group with identification of a Principal Investigator, Statistical Investigator, and any co-investigators. Submitted proposals for genomic characterization must be for use of biospecimens collected from cancer treatment trials led by an NCTN Network Group and stored in an NCI-funded Network Group Biospecimen Bank. Proposals must be from trials in which the clinical data will be mature and available within 6 months of proposal selection.
* Examples of eligible cancer treatment trials include those thattest the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person’s immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.
* Proposals are not limited to a particular trial phase (i.e., pilot, phase 1, phase 2, and phase 3 trials are all eligible).

**B. Ineligible proposals**

* Studies proposing analysis of specimens collected from trials other than those listed under “Eligible proposals” above
* Proposals not submitted by an NCTN Network Group
* Trials with inadequate consents to cover the use of specimens for the outlined research

**VI. Proposal Package & Submission**

**What is required?**

* A *cover letter* signed by the NCTN Network Group Chair (i.e., contact PI for the NCTN Network Group Operations Center U10 grant) indicating submission of a proposal in response to this NCI Clinical Trial Sequencing Project (CTSP) Announcement.

**The cover letter should include:**

* Title of the proposed study
* Brief description of the proposed study with reference to whether clinical data is already available or date it is expected to be available
* Total budget figure projected for the study if funds are being requested for locating, assessing, preparing, or shipping biospecimens to NCI CCG.
* Expected duration of the study
* *Proposal,* described using the Proposal Form provided in Section XI,shouldnot exceed 10 pages, excluding any necessary illustrations, appendices, and/or any budget request submitted to cover biospecimen location, assessment, preparation, and shipment to NCI. Proposals should follow the attached form, and should contain the following elements:
* A description of how genomic information could help address a key clinical question(s)
* Statistical considerations regarding the ability to answer the question with the samples available
* Number of samples, including sample formats
* *Budget* as described in the **Budget Preparation** section (below), if additional costs as described in the first paragraph of Section IV above are being requested.
* The latest version of the parent *NCTN clinical trial protocol* (for reviewer reference).

**Budget Preparation for Requests for Funding to Cover Locating, Assessing, Preparing, and/or Shipping of Biospecimens to NCI CCG (if costs are NOT covered by the NCTN Network Group tumor banking grant)**

* The budget must clearly detail the costs (Direct and Indirect) related to the activity for which the funding is being requested and which is needed for the conduct of the proposed study.
* The budget for the study should use the Form PHS 398 along with a narrative justifying each requested cost (<http://grants.nih.gov/grants/funding/phs398/phs398.html>).
* Covered costs are limited to activities related to locating, assessing, preparing, or shipping specimens to NCI CCG.
* Costs for the P.I. for the proposal and/or Network Group leadership are **not** covered under this project.
* At the time of initial submission of a budget request, the signature of the institutional business official is not required. Institutional approval and sign-off will be required, however, if the proposal is selected and funding for these additional costs is approved by NCI.

**Proposal Package Submission**

A complete Proposal Package, consisting of a Cover Letter, Proposal Form including attachments, and Budget (if requested), must be emailed via pdf attachment by the NCTN Network Group Operations Center to:

NCI CTEP Protocol and Information Office – PIO@ctep.nci.nih.gov

cc: Margaret Mooney, M.D. – mooneym@ctep.nci.nih.gov

Email submissions must reference “NCI Clinical Trial Sequencing Project (CTSP) Proposal” in the Subject line.

**VII. Terms and Conditions for Funding Additional Costs**

Funds to cover the genomic characterization required for selected/successful proposals will be covered by the NCI Center for Cancer Genomics (CCG). Funds for any additional costs associated with the proposals related to locating, assessing, preparing, or shipping specimens to NCI (if not covered by the NCTN Network Group tumor banking award) will be provided via the parent U10 Cooperative Agreement grant for the Network Group Operations Center and will be administered by CTEP in consultation with CCG. All the terms and conditions of the parent U10 award apply to this funding. Supplement recipients will be required to provide an annual progress report to CTEP/CCG. Funding is restricted for the purpose of the approved project. Similarly, any carryover requests for this funding are limited to the approved project unless written approval is obtained in advance by the NCI NCTN Program Director in consultation with CCG.

**VIII. Submissions Required After Proposal Approval**

Investigators with approved proposals will be asked to submit the following to NCI CCG:

*Regulatory documents:*

1. **Material Transfer Agreement.** A fully executed Material Transfer Agreement (MTA) with Nationwide Children’s Hospital in Columbus, Ohio, to allow for receipt and processing of biospecimens, as well as distribution of analytes to characterization centers. If desired, an MTA template can be provided upon request. (To request a template, please email Julia Zhang at jiashan.zhang@NIH.GOV.)
2. **Certification of consent.** 1) A blank consent form from the associated clinical trial; 2) Institutional Review Board (IRB) approval or waiver for the research study; and 3) an Institutional Certification stating that the patients have been consented to allow, at a minimum, use of their samples for general research use. Ideally, the consent should allow for genomic research (DNA/RNA sequencing).

*Biospecimens:*

1. **Tumor tissue.** Either fresh frozen or formalin-fixed paraffin-embedded (FFPE) material will be acceptable. Tumor biopsy is acceptable (excisional or core needle, but not fine needle aspirate). The quantity of biopsy material needed will vary according to the size and cellularity of the biopsy specimen. For excisional biopsies of ~1 cm2 cross-sectional area, 10 x 10 micron sections of FFPE or frozen tissue would be required, with the number of sections scaled up or down based on the cross-sectional area. For core needle biopsies, an entire core is required. Although fresh frozen is optimal, it is not required.

**Note:** These amounts of tissue are anticipated to yield the > 3 micrograms of DNA and RNA needed for the analysis. Submitting more rather than less tissue will increase the likelihood of NCI CCG obtaining > 3 micrograms of nucleic acid from the tissue.

1. **Non-tumor matched tissue.** Optimally, a matched non-tumor sample from the same patient should also be submitted. Ideally, this would be 5 ml of frozen blood. If that is not available, then buccal swabs, peripheral blood mononuclear cells (PBMCs), or a piece of tissue taken from a different organ from which the tumor tissue was excised (skin, spleen, etc.) can be accepted.
2. **An H&E diagnostic slide**, taken from a piece proximal to the tumor tissue being submitted. The actual slide can be substituted by an Aperio (or similar) scan of the slide at 40x magnification.
3. **Other biomarker data.** If the specimens are annotated with additional correlative data, for example standard IHC biomarkers, this information should also be provided.

*Data:*

1. **Pathology report(s).** A de-identified (PHI-censored) copy of the original pathology report created at the tumor excising institution. If central pathology review was conducted on the specimen, the pathology report from the central review should also be sent, in addition to the local pathology report. (PHI: Protected Health Information)
2. **Clinical and outcome data.** Mature clinical data and outcome data relevant to the key question of the study must be submitted. These clinical and outcome data need to be deposited into the Open Clinica system maintained by the Biospecimen Core Resource (BCR) of the NCI CCG at Nationwide Children’s Hospital in Columbus, Ohio, no later than 6 months after approval of the proposal.

**IX. Publication and Data Sharing**

Investigators with an approved study must agree to publish the results from their study within one year following completion of the molecular/genomic data characterization.

A writing committee should be formed that is co-chaired by the P.I. of the study team from the NCTN Network Group (or the P.I.’s designee) and the Lead Scientist involved in the genomic data analysis. The P.I. (or designee) and the Lead Scientist will serve as the senior authors. Other members of the writing committee, who would serve as co-authors, should include investigators involved substantially in the clinical trial analysis and in the genomic characterization and analysis.

Upon completion of the study, publications should acknowledge the funding source as follows:

*“This clinical study was supported in whole or in part by funding from the National Cancer Institute (NCI) under the NCI Clinical Trial Sequencing Project.”*

Upon publication, the study’s clinical, outcome, and genomic data must be submitted to a controlled-access database approved by NCI (e.g., dbGaP), through which the data will be made available to qualified researchers who sign appropriate data use agreements.

**X. Inquiries**

Questions regarding responsiveness of the proposed studies to this Announcement should be directed to one of the following NCI Program Staff:

**Scientific Contact:**

Jean Claude Zenklusen, Ph.D.

Director, The Cancer Genome Atlas Program Office

National Cancer Institute

31 Center Drive

Suite 3A20

Bethesda, MD 20892

Phone: 301-451-2144

Email: jz44m@nih.gov

**Administrative Contact:**

Margaret Mooney, M.D.

Program Director, National Clinical Trials Network

Chief, Clinical Investigations Branch

Cancer Therapy Evaluation Program

National Cancer Institute

9609 Medical Center Drive

Room 5W-412

Bethesda, MD 20892-9737

ROCKVILLE MD 20850-9737

Phone: 240-276-6560

Email: mooneym@ctep.nci.nih.gov

**XI. PROPOSAL SUBMISSION FORM**

**1. Date submitted:** [Single-click here to add text]

# 2. Title of proposed study: [Single-click here to add text]

# *(Your study title should be as descriptive as possible, similar to the level of descriptiveness required for titles of clinical trials.)*

# 3. NCTN Network Group

Name of NCTN Network Group submitting proposed study: [Single-click here to add text]

Name of Contact PI for NCTN Network Group Operations Center: [Single-click here to add text]

# 4. Principal Investigator

Name of Principal Investigator for NCTN Network Group proposed study: [Single-click here to add text]

Suffix (e.g., M.D., Ph.D.): [Single-click here to add text]

Institution: [Single-click here to add text]

Mailing address: [Single-click here to add text]

Email: [Single-click here to add text]

Phone: [Single-click here to add text] Fax: [Single-click here to add text]

# 5. Statistical investigator

Name: [Single-click here to add text]

Suffix (e.g., M.D., Ph.D.): [Single-click here to add text]

Institution: [Single-click here to add text] Email: [Single-click here to add text]

Phone: [Single-click here to add text] Fax: [Single-click here to add text]

# 6. Co-investigators

(Note: Only those investigators who have had/will have substantive input into the design, development, and/or conduct of your proposed study should be listed below.)

Name: [Single-click here to add text] Network Group affiliation: [Single-click here to add text]

Suffix (e.g., M.D., Ph.D.): [Single-click here to add text]

Institution: [Single-click here to add text] Email: [Single-click here to add text]

Name: [Single-click here to add text] Network Group affiliation: [Single-click here to add text]

Suffix (e.g., M.D., Ph.D.): [Single-click here to add text]

Institution: [Single-click here to add text] Email: [Single-click here to add text]

Name: [Single-click here to add text] Network Group affiliation: [Single-click here to add text]

Suffix (e.g., M.D., Ph.D.): [Single-click here to add text]

Institution: [Single-click here to add text] Email: [Single-click here to add text]

#### 7. Clinical trial

Protocol number(s) and protocol title(s) of the trial(s) from which specimens would be sent:

[Single-click here to add text]

*Note: If you are requesting sequencing of specimens from more than one trial, your proposal should provide a clear rationale for including samples from different trials.*

###### 8. Description of specimens (for both tumor and any matched normal biospecimens)

Tissue/specimen type *(e.g., FFPE malignant primary tumor tissue)*: [Single-click here to add text]
Number of samples (cases): [Single-click here to add text]

Existing biomarker annotation, if any: [Single-click here to add text]

Tissue/specimen type *(e.g., FFPE malignant primary tumor tissue)*: [Single-click here to add text]
Number of samples (cases): [Single-click here to add text]

Existing biomarker annotation, if any: [Single-click here to add text]

Tissue/specimen type *(e.g., FFPE malignant primary tumor tissue)*: [Single-click here to add text]
Number of samples (cases): [Single-click here to add text]

Existing biomarker annotation, if any: [Single-click here to add text]

Tissue/specimen type *(e.g., FFPE malignant primary tumor tissue)*: [Single-click here to add text]
Number of samples (cases): [Single-click here to add text]

Existing biomarker annotation, if any: [Single-click here to add text]

Would all cases from the trial be sent for genomic characterization, or select cases?

[ ]All cases from the trial

[ ]Select cases

If select cases,describe the inclusion/exclusion criteria:

[Single-click here to add text]

**9. Study question**

Describe how the genomic information could help address a key clinical question(s). In your response, please also briefly describe the clinical trial(s) and its results, if available: [Single-click here to add text]

What are your hypotheses? [Single-click here to add text]

What are your objectives? [Single-click here to add text]

Precisely define the endpoints that are the subject of the study’s objectives, specifically indicating the events included in each endpoint definition: [Single-click here to add text]

Primary comparisons: [Single-click here to add text]

Is the relevant clinical and outcome data for the study question available? [Single-click here to add text]

If not, when is it expected to be available? [Single-click here to add text]

#### 10. Background data

Please provide any relevant background data. Briefly include relevant data in the published literature and the clinical importance of having this question addressed.

[Single-click here to add text]

## **11. Statistical analysis plan**

In your statistical analysis plan, please provide the following, as applicable, and if not already answered above:

* Statistical methods for the main analyses (e.g. Cox proportional hazards regression, conditional logistic regression, etc.)
* Sample size estimate and statistical power
* Transformations applied to variables
* Variable selection procedures (including a list or description of the variables initially considered for inclusion in the model)
* List of standard clinical variables to be incorporated into models or other analyses
* Multiple-comparisons adjustment methods
* Any other information necessary for the review committee to understand and evaluate the main analyses you are proposing

Statistical analysis plan: [Single-click here to add text]

**12. Budget**

Please provide a budget if funding is being requested for locating, assessing, preparing, and/or shipping biospecimens to NCI (if not covered under the NCTN Network Group Banking grant) using the PHS 398 ( form and instructions available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> ) as described under “Budget Preparation” in the Announcement above.

Appendices

You may provide further detail/illustrations on your proposed study in appendices to this form.