**NOTE:** Minor change made 12/15/2020 to clarify in the eligibility section that eligible trials must be fully accrued.

**Announcement to NCTN Network Groups & NCORP Research Bases**

**National Cancer Institute (NCI)** **Molecular Profiling to Predict Response to Treatment (MP2PRT) Program: Retrospective Characterization and Analysis of Biospecimens Collected from NCI-Sponsored Trials of the National Clinical Trials Network (NCTN) Groups and NCI Community Oncology Research Program (NCORP) Research Bases**

**Key Dates**

**Release Date: Wednesday, December 2, 2020**

**Webinar: Friday, December 11, 3-4 PM Eastern**

**Receipt Dates for Proposals: Monday, March 15, 2021**

**I. Purpose**

This announcement is associated with the  [Cancer MoonshotSM Initiative](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative) that is intended to accelerate cancer research. Specifically, this announcement targets the following area designated as a scientific priority by the Blue Ribbon Panel (BRP):

The Clinical Trials Working Group of the BRP recommended retrospective analysis of biospecimens already collected from patients enrolled on completed NCI-sponsored clinical trials of the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) that have outcome results available.

The generation of comprehensive molecular characterization data that can be paired with standardized treatment and outcome data from patients enrolled on clinical trials will create a valuable resource for future qualified researchers. We particularly encourage proposals that seek to fill gaps in currently available characterization data, enhance our understanding of rare cancer types or sub-types or issues such as minimal residual disease in solid tumors, and/or enhance our understanding of cancer in racial/ethnic minority groups or underserved populations.

This is the third announcement for this program. It is expected that up to four proposals from the NCTN Groups and NCORP Research Bases will be funded with this announcement.

**II. Overview and Summary**

NCI convened the Blue Ribbon Panel (BRP) in 2016 to provide recommendations for achieving the Cancer Moonshot's ambitious goal of making a decade's worth of progress in cancer research in 5 years, now called the  [Cancer MoonshotSM Initiative](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative). The BRP was charged with assessing the state of the science in specific areas and identifying major research opportunities that could uniquely benefit from the support of the Cancer Moonshot and could lead to significant advances in our understanding of cancer and in how to intervene in its initiation and progression. The recommendations focused on areas in which a coordinated effort could profoundly accelerate the pace of progress in the fight against cancer and were not intended to replace existing cancer programs, initiatives, and policies already underway. The [BRP final report](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel/blue-ribbon-panel-report-2016.pdf) was approved by the National Cancer Advisory Board and included a recommendation for Retrospective Analysis of Biospecimens. The [21st Century Cures Act](https://www.congress.gov/bill/114th-congress/house-bill/6) was signed into law in December 2016 dedicating new funds to support efforts associated with the  [Cancer MoonshotSM Initiative](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative), including support for this announcement.

The NCI invites funded NCTN Network Groups (NCTN Operations Centers in conjunction with the NCTN Biospecimen Banks, NCTN Statistics & Data Management Centers (SDMCs), and relevant group of NCTN investigators) and NCORP Research Bases to submit proposals requesting characterization of biospecimens collected from NCI-sponsored NCTN or NCORP clinical trials. These trials must be fully accrued with clinical data (either the primary outcome or other relevant clinical outcomes data) already presented or published, or for which publication or presentation at a major scientific meeting is **expected within eighteen months of March 15, 2021**. However, if clinical outcome data are required to inform the case selection or are needed for any reason before the proposed molecular characterization can be accomplished, these data must be available in time to **complete the proposed project within two years**.

The MP2PRT seeks proposals that are **exploratory**, **hypothesis-generating**, or **hypothesis-driven**, and that propose studies wherein comprehensive molecular analyses could answer a key clinical question or lead to additional important clinical research or trial designs.

This program will use contracted laboratories to perform molecular characterization approaches such as whole genome sequencing (WGS), whole exome sequencing (WES), transcriptome sequencing (RNASeq), immunotherapy marker analysis, circulating tumor DNA analysis (ctDNA), or other molecular assays as required by the approved proposals to generate the data relevant to the hypothesis(es) submitted by the investigators. The samples will be identified, prepared, and submitted for characterization by the appropriate NCTN Biospecimen Banks.

Data analysis will be performed as a collaboration between the NCTN Network Group or NCORP Research Base and its investigators submitting the proposal, the investigators at the contracted laboratories who characterize the samples, and investigators at contracted genomic data analysis centers (if needed). The NCTN Network Group or NCORP Research Base will be responsible for providing the clinical data to the NCTN/NCORP Data Archive (as needed, and other appropriate archives as needed) and submitting subsets of the data needed for the proposal to an appropriate NCI controlled-access database (e.g., NCI Genomic Data Commons) for analysis. The project team (Network Group or Research Base/investigators and contractors) will analyze the data together.

Clinical and molecular characterization data related to and resulting from the analyses will need to be made publicly available to qualified researchers via an appropriate NCI controlled-access database (e.g., NCI Genomic Data Commons and any databases required for Cancer MoonshotSM Initiative projects) upon open access publication of the primary analysis described in the study proposal.

If clinical images were collected as part of the clinical trial, then this program will provide support to the NCTN Network Group or NCORP Research Base to prepare and submit relevant clinical images to an appropriate database as part of the clinical data sharing. This will enhance the future research that can be done by pairing information from the clinical data, characterization data, and clinical images.

**III. Evaluation Process**

Proposals will be reviewed by NCI for scientific merit, feasibility of the work, and potential for benefiting patients and guiding future treatment decisions.

Based on the BRP recommendations, projects of particular interest to accelerate our understanding of biologic response include:

* Analyses in rare tumor types (e.g., head and neck cancer)
* Analyses in special populations (e.g., racial/ethnic minority groups and underserved populations)

Proposing NCTN Network Groups or NCORP Research Bases should expect to receive a decision on their proposal within four months of proposal submission. Proposals that NCI recommends for funding will likely be required to submit a revised proposal to address reviewer feedback before receiving final approval. Proposed projects should be able to be completed within two years of executing subcontracts with the NCI contractor, Leidos Biomedical Research, Inc, as described below.

**Criteria for Review of Proposals**

Prioritization and evaluation of proposals will include the following considerations:

* Inclusion of comprehensive molecular analyses which will answer a key clinical question(s) or fill a gap in existing data and generate valuable data for future research
* Ability to address the study hypothesis(es) and/or achieve the study’s hypothesis-generating or exploratory goals with the number and quality of biospecimens available
* Inclusion of an appropriate statistical plan for the proposed project, whether exploratory, hypothesis-generating, or hypothesis-driven, with sufficient detail to assure reviewers that the investigators will be capable of carrying out the project
* Ability of the proposed study to fill a gap in our understanding of health disparities in a special population(s)
* Appropriate consents were obtained from patients on study for use of the specimens for future unspecified research
* Acceptable plans for addressing the Cancer MoonshotSM Initiative Public Access and Data Sharing Policy (e.g. the NCTN/NCORP Data Archive, NCI Genomic Data Commons)
* Acceptable timelines for provision of biospecimens for characterization, availability of clinical data, and execution of data sharing plans

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**

The NCI MP2PRT program will be managed through DCTD. A **contract mechanism** will be used to fund the MP2PRT program, including the molecular characterization and data analyses.

Funding should be requested by applicants as part of the proposal budget to cover costs **not** already covered by existing NCTN/NCORP grants. The funding for approved proposals will be provided via a **subcontract** mechanism to the NCORP Research Base or via **separate subcontracts** to the NCTN Group Operations, SDMC, and Bank components.

Because this program uses a contract mechanism, selected proposals will be approved **contingent upon successful negotiation of the necessary subcontracts** with the NCI contractor, Leidos Biomedical Research, Inc. These subcontracts will describe all investigator and Group responsibilities for the completion of the proposed project. Please note that the subcontract process involves submitting Technical and Cost Proposals for the necessary subcontracts to Leidos Biomedical Research, Inc., and fully executing all necessary subcontracts. The subcontract negotiation and execution processes typically take 4-6 months following proposal selection.

It is anticipated that the total funding for the non-Bank, non-imaging components of the proposal will be between $100,000 and $300,000 per proposal, depending on the costs and effort required and described in the budget proposal. Funding for the Bank components of the proposal will be dependent on both the number of cases and specimens required and the type of specimen preparation needed. Funding to support preparation and submission of clinical images to an appropriate database, if requested, will be based on the number of images and type of preparation required.

For this announcement, the number of anticipated proposals selected is contingent upon the number of meritorious proposals submitted and the availability of funds. Up to four proposals are expected to be selected based on anticipated available funding. 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 U.S. NCTN Network Group or NCORP Research Base with identification of a Clinical Principal Investigator, Statistical Investigator, Biospecimen Bank PI, and any co-investigators.
* Proposals must be for use of biospecimens collected from **fully accrued** cancer trials led by an NCTN Network Group and stored in an NCI-funded Network Group Biospecimen Bank or cancer trials led by an NCORP Research Base and stored in a central NCI-funded biospecimen bank.
* Proposals must be from trials for which clinical data have already been presented or published, or for which publication or presentation at a major scientific meeting is **expected within eighteen months of March 15, 2021**. However, if clinical trial data are required to inform the case selection or are needed for any reason before the proposed molecular characterization can be accomplished, these data must be available in time to **complete the proposed project within two years**.
* Proposals must include a budget as described in the **Budget Preparation** section below with a detailed narrative justification for each budget section providing details about all included costs and confirmation that the indirect cost rates applied are the appropriate rates for a contract mechanism.
* Proposals must include letters of support from the **Statistical Investigator** verifying the availability of the relevant data for sufficient patients with the relevant consent under standard DUA terms and from the **tumor bank** verifying the availability of the specimens for transfer for the project under standard MTA terms.

**B. Ineligible proposals**

* Studies proposing analysis of specimens collected from trials other than those listed under “Eligible proposals” above
* Proposals not submitted by a U.S. NCTN Network Group or NCORP Research Base
* Trials with inadequate specimens for the outlined research
* Trials with inadequate consents to cover the use of specimens for the outlined research
* Trials with unacceptable timelines for provision of both biospecimens and clinical data

**VI. Pre-Application Webinar**

A pre-application webinar will be held on Friday, December 11, 2020 from 3:00 PM to 4:00 PM Eastern Time to discuss this Announcement, highlight key changes from the previous announcements, and answer questions from potential applicants. Please use the WebEx information below to join this webinar. Slides from the pre-application webinar will be available at <http://ctep.cancer.gov/initiativesPrograms/nctn.htm> within one week of the webinar.

**MP2PRT 3rd Round Webinar**

Friday, Dec 11, 2020 3:00 pm | 1 hour | (UTC-05:00) Eastern Time (US & Canada)

**Join online to view the presentation and listen to the audio**

<https://cbiit.webex.com/cbiit/j.php?MTID=m73f67413e98f98e4fd4130b132033475>

Meeting number: 180 393 1277

Password: ZxxQmpN?497

**Join by phone**

1-650-479-3207 Call-in toll number (US/Canada)

Access code: 180 393 1277

**VIII. 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) or NCORP Research Base PI indicating submission of a proposal in response to this NCI Molecular Profiling to Predict Response to Treatment (MP2PRT) Program Announcement.

**The cover letter should include:**

* Title of the proposed study and title of the clinical trials from which specimens and clinical data will be used
* Brief description of the proposed study with reference to whether clinical data are already available or when they are anticipated to be available
* **Total budget figure** projected for the study (total contract costs, including both direct and indirect contract costs)
* **Sub-total budget figures** projected for the **Operations**, **SDMC**, and **Biospecimen Bank** components of the project as applicable (total contract costs)
* *Proposal,* described using the Proposal Form provided in Section XII,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 why molecular characterization of the proposed patient population is of clinical interest
* How the proposed molecular characterization could help answer a clinical question or otherwise fill a gap in the existing data or enhance our understanding of the population
* Statistical considerations regarding the ability to answer the question or advance the field with the samples available
* Number of samples, including sample formats
* Proposed molecular characterization techniques
* Timelines for provision of biospecimens and clinical data from the time of notification of award
* *Budget* as described in the **Budget Preparation** section (below)
* *Letter of Support* from the Statistical Investigator. Letter should include:
	+ Number of patients with appropriate consent and requested specimens available
	+ Verification that all relevant data will be able to be appropriately processed and transferred for collaborative analysis under standard DUA terms and within the proposed timeline
	+ Sub-total budget figures (both direct and total for the entire project) for the funding requested for preparing and transferring relevant patient-level clinical and outcome data
	+ Verification that the requested funding is not covered by existing NCI grants and will cover the anticipated data costs
* *Letter of Support* from the Biospecimen Bank PI. Letter should include:
	+ Number of patients with appropriate consent and requested specimens available
	+ Verification that relevant specimens will be able to be appropriately processed and transferred to the contracted laboratory under standard MTA terms and within the proposed timeline
	+ Sub-total budget figures (both direct and total for the entire project) for the funding requested for locating, assessing, preparing (i.e. analyte extraction), and shipping biospecimens as well as providing the necessary biospecimen information for the NCI database
	+ Verification that the requested funding is not covered by existing NCI grants and will cover the anticipated bank costs

**Budget Preparation**

**Separate budget sections** should indicate which costs would be paid to each NCTN Group component. Thus, for NCTN Group proposals there should be three budget sections: one budget section and justification for the Operations component, one budget section and justification for the SDMC component, and one budget section and justification for the Biospecimen Bank component. For the NCORP Research Bases there should be a single budget. **A detailed narrative justification for each budget section, including the total costs for each section, should provide details and rationale for all included costs and should confirm that the indirect cost rate applied is the rate used for contracts.**

The budget may include costs for locating, assessing, preparing, and shipping of biospecimens to the contracted laboratory; costs for preparation and transfer of relevant patient-level clinical and outcome data from the trial(s) to the appropriate data repositories; costs to support reasonable biostatistician, lead investigator, and operations staff involvement in the proposed research project; and costs to support the preparation and submission of clinical images to an appropriate database.

The budget must NOT include costs covered by any NCTN or NCORP grant.

**Please note that funding for approved proposals will be provided via a contract mechanism, rather than a grant supplement. Proposal budgets should be prepared accordingly, including the appropriate indirect cost rates.**

* The budget must clearly detail the total costs (both 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 should use the Form PHS 398 along with a narrative justifying each requested cost (<http://grants.nih.gov/grants/funding/phs398/phs398.html>). A separate Form PHS 398 and narrative justification should be submitted for each NCTN Group grant component.
* Because this program will be conducted through **sub-contracts**, the budget should clearly identify how much funding is being requested for each distinct institution. If the proposal includes preparation (e.g., deidentification) and submission/transmittal of clinical images, then the budget should clearly identify the funding being allocated to this purpose, including any funding that will be distributed through a subcontract from the NCTN Group to IROC or other institutions, if applicable.
* Covered costs are limited to the activities described above.
* 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 through the subcontract mechanism.

**Proposal Package Submission**

A complete Proposal Package, consisting of a Cover Letter, Proposal Form including Budget, Letters of Support, and attachments must be emailed via pdf attachment by the NCTN Network Group Operations Center or NCORP Research Base to:

Margaret Mooney, M.D. – NCINCTNRFA@mail.nih.gov

Email submissions must reference “NCI MP2PRT Proposal” in the Subject line. Place all documents (cover letter, proposal, budget letters of support, and other attachments) into a single PDF packet for the submission. Do not use protected mode on the PDF or send a total image scan of the packet.

**X. Publication and Data Sharing**

Investigators with an approved study must agree to publish the results from their study within 1 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 molecular characterization 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 molecular 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*  [Cancer MoonshotSM Initiative](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative)*.”*

Upon publication, in accordance with the Cancer MoonshotSM Initiative Public Access and Data Sharing Policy, 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.

**XI. Inquiries**

Questions regarding responsiveness of the proposed studies to this Announcement should be directed to one of the following NCI Program Staff via the NCINCTNRFA@mail.nih.gov email:

**Scientific Contacts:**

Margaret Mooney, M.D.

Program Director, National Clinical Trials Network

Chief, Clinical Investigations Branch

Cancer Therapy Evaluation Program

National Cancer Institute

NCINCTNRFA@mail.nih.gov

Irina Lubensky, M.D.

Chief, Pathology Investigation and Resources Branch

Cancer Diagnosis Program

National Cancer Institute

NCINCTNRFA@mail.nih.gov

**Administrative Contact:**

Grace Mishkin, MPH

NCTN Operations

Clinical Investigations Branch

Cancer Therapy Evaluation Program

National Cancer Institute

NCINCTNRFA@mail.nih.gov

**XII. 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 must reference the protocol number[s] of the clinical trial[s] from which you are proposing to use biospecimens, and should be as descriptive as possible, similar to the level of descriptiveness required for titles of clinical trials.*

**3. Abstract:**

Please provide an abstract of your proposal in no more than 300 words that highlights the key clinical question(s) or objectives addressed by your proposal:[Single-click here to add text]

# 4. NCTN Network Group/ NCORP Research Base

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

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

# 5. Principal Investigator

Name of Principal Investigator for 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]

# 6. 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]

# 7. Biospecimen Bank 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]

# 8. Co-investigators

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. Provide a **letter of collaboration** as an attachment from each listed co-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]

State, Country: [Single-click here to add text]

Email: [Single-click here to add text]

Network Group affiliation (if any): [Single-click here to add text]

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]

State, Country: [Single-click here to add text]

Email: [Single-click here to add text]

Network Group affiliation (if any): [Single-click here to add text]

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]

State, Country: [Single-click here to add text]

Email: [Single-click here to add text]

Network Group affiliation (if any): [Single-click here to add text]

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]

State, Country: [Single-click here to add text]

Email: [Single-click here to add text]

Network Group affiliation (if any): [Single-click here to add text]

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]

State, Country: [Single-click here to add text]

Email: [Single-click here to add text]

Network Group affiliation (if any): [Single-click here to add text]

#### 9. Objectives

What are the objectives? *(Please distinguish any primary and secondary objectives.)*

[Single-click here to add text]

#### 10. Hypotheses

What are the specific hypotheses or goals of the study? If the study is hypothesis-generating or exploratory, please indicate that.

[Single-click here to add text]

###### 11. Preliminary data and study justification

Please briefly describe the background and significance of your study objectives. If the objectives are hypothesis-generating or exploratory, please describe why these objectives are important.

[Single-click here to add text]

Please provide preliminary data on any proposed classifier(s) or markers that motivate the primary objectives and/or justify the need for performing molecular characterization in this study.

[Single-click here to add text]

#### 12. Clinical trial(s)

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. If you are requesting specimens from a legacy banking trial associated with one or more treatment trials, provide information about both the banking trial as well as all associated treatment trials from which specimens and clinical data would be obtained.***

Number of cases for whom biospecimens were obtained in the trial(s): [Single-click here to add text]

Why are biospecimens from this clinical trial or trials necessary to complete your proposal? In your response, please briefly describe the trial(s) and its results, if available:

[Single-click here to add text]

###### 13. Narrative description of proposed study

Please provide a brief narrative description (no more than 1 page) of the number and type of biospecimens and cases being requested, the proposed characterization that would be done on each type of biospecimen/case, and the analyses that would be conducted. This narrative should include the answers to some of the more detailed questions asked in sections 14-21, but please also add other information or context you believe it would be helpful for us to know in reviewing your proposal. The purpose of this narrative description is to clearly lay out what specimens you propose to use and what characterization and analyses you propose to conduct if your proposal is selected.

[Single-click here to add text]

###### 14. Description of specimens

Number of patient cases for whom molecular characterization is requested as part of this proposal: [Single-click here to add text]

What tissue/biospecimen types are you requesting molecular characterization for? *(e.g., FFPE malignant primary tumor tissue)*:

[Single-click here to add text]

Required number of biospecimens per specimen type: [Single-click here to add text]

***Note: If you are requesting sequencing of specimens from more than one trial, your proposal should answer the following three questions separately for each trial from which you are requesting specimens.***

How many cases in the trial currently have biospecimens? [Single-click here to add text]

How many cases are requested for use in this proposal? [Single-click here to add text]

How many cases will have material left for future studies if the requested biospecimens are provided for this study? [Single-click here to add text]

Will this study exhaust any existing biospecimen resources (e.g., tissue blocks, archived unstained slides, blood/products)? Describe the number, type, timepoints, and patient characteristics of any biospecimen resources that will be exhausted. [Single-click here to add text]

Required number and thickness of sections from each biospecimen (if solid tissue is requested):

[Single-click here to add text]

# Required amount of other type of biospecimen(s) (if biospecimens other than solid tissue are requested): [Single-click here to add text]

Does pathology need to be performed on any of the biospecimens prior to analyte extraction? If so, briefly describe the biospecimens that will require review and the pathology review that will be required, and ensure any associated costs are clearly described in the appropriate budget:

[Single-click here to add text]

# Will tumor enrichment (e.g. microdissection, FACS) be required prior to analyte extraction?) If so, briefly describe the biospecimens that will require enrichment and the enrichment required, and ensure that any associated costs are clearly described in the appropriate budget: [Single-click here to add text]

# Is there any other information about the biospecimens that would be helpful for the proposal reviewers or the contract team to know? [Single-click here to add text]

#### 14. Laboratory methods

Molecular characterization will be performed by contracted laboratories selected through standard processes by the NCI contractor for this project. Your responses to this section will help us evaluate your scientific proposal and potentially estimate the funding needed to carry out the proposed work through this contract mechanism.

Describe the anticipated characterization methods needed for this proposal, including required levels of coverage and any special extraction, preparation, or characterization requirements (e.g., library preparation kits, sequencing protocols and platforms) that may affect the cost of the proposed specimen preparation and characterization. If the proposed characterization has only been done in a small number of laboratories, please list the laboratories you are aware of that could complete the proposed project. If the proposed preparation or characterization is relatively new, please include references to papers describing the methods: [Single-click here to add text]

#### 15. Facilities & personnel

Briefly identify who will be responsible from the NCTN Group or NCORP Research Base for the **statistical** **and** **bioinformatic analyses** of the data that will be generated in the proposed study and describe each individual’s role:[Single-click here to add text]

Will additional bioinformatic analysis expertise (from personnel not listed above) be required to carry out the proposed project? If so, please describe the anticipated needs: [Single-click here to add text]

Do the proposed personnel have facilities with the capacity and security to store and analyze all genomic data? This is not required, but if the proposed personnel have this capacity, please describe: [Single-click here to add text]

#### 16. Endpoints/Outcomes (as applicable)

Precisely define the endpoints that are the subject of the study’s main objectives; for time-to-event outcome variables, be sure to clearly indicate the types of events included in each endpoint definition. For **exploratory** objectives, please clearly describe the proposal goals:

[Single-click here to add text]

#### 17. Case selection

As applicable, specify the proposed case selection method, including inclusion/exclusion criteria, and whether stratification or matching will be used, or state if you simply request biospecimens from all cases with adequate biospecimen available. If a complex case selection strategy (e.g., matched or adaptive selection) will be used, then the specific algorithm should be described:

[Single-click here to add text]

18. Statistical analysis plan for addressing the primary objectives

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

Note: If the proposal is **hypothesis-driven**, describe how the primary objectives will be addressed in a quantifiable and statistically evaluable way.

For **hypothesis-generating** and **exploratory proposals**, include an appropriate and sufficiently detailed statistical plan to allow the reviewers to assess the value of the proposed hypothesis-generating/ exploratory analyses. Indicate the specific quantities that will be evaluated and the general statistical framework (e.g., estimation, association, comparison, prediction).

In your statistical analysis plan, please also provide the following, as applicable

* Statistical methods for the primary analyses (e.g., Cox proportional hazards regression, conditional or unconditional logistic regression, etc.).
* Transformations applied to variables.
* Methods for classifier and/or marker cutpoint validation.
* 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.
* For complex studies, methods that will be used to validate the analysis results, or a rationale for not performing a validation study.

Any other information necessary for the statistical reviewers to understand and evaluate the primary analyses you are proposing.

#### 19. Statistical justification for sample size (as applicable)

Based on the stated primary analyses and proposed statistical analysis plan, provide a justification (rationale) for the requested number of biospecimens.

**Sample size estimate:** [Single-click here to add text]

*(e.g., number of cases required to achieve adequate statistical power or certainty of estimation; need for number of cases for proposed exploratory project)*

**Rationale for the sample size estimate:** [Single-click here to add text]

Note: For **hypothesis-generating** and **exploratory** **proposals**, it is understood that there may not be adequate power to assess all proposed exploratory aims. Therefore, please state if you simply request biospecimens from all cases with adequate biospecimen available or if your sample size is based on another rationale. For projects requesting characterization of a large number of specimens, it is recommended that example power calculations be provided if any statistical inference will be reported.

**For hypothesis-driven proposals**, the rationale should include a clear explanation (or cited reference) for the method of sample size determination along with a statement of all assumptions required to perform that calculation so that an independent statistician would be able to reproduce the estimates from the information provided in the application.

Typically, a sample size estimate will require assumptions about the following:

* Anticipated distribution of classifier/marker values in the targeted population(s) (e.g., marker positivity rate if the marker is dichotomous)
* Assay success rates (based on anticipated rates of technical failures, degraded or insufficient biospecimens, etc.)
* Event rates or number of events anticipated for the cases included in the primary analysis
* Expected differences in outcomes or magnitudes of associations (e.g., hazard ratio or other “effect” size)

For **hypothesis-driven proposals**, these assumptions and estimates need to be supported by preliminary data or previous studies that should be described either in this section or in the background section.

20. Statistical considerations for secondary objectives (if applicable)

Detailed statistical considerations for addressing your secondary objectives are typically not required, but a general description of the intended approach (e.g., Cox proportional hazards regression modeling) should be provided **as applicable**.

However, if your secondary objectives involve very large numbers of analyses (e.g., examining association of expression of thousands of individual genes with a clinical endpoint) or will consume large amounts of biospecimens, please provide more detail to justify that the proposed analyses will be a productive use of the resource and not generate an unacceptably large number of spurious results.

Statistical considerations for secondary objectives (**if applicable**):

[Single-click here to add text]

21. Clinical images (if applicable)

If clinical images were collected as part of the clinical trial(s), this program will also provide support to prepare and submit relevant clinical images to an appropriate database and thus enhance the future research that can be done by pairing information from the clinical data, characterization data, and clinical images.

Are you requesting support to prepare and submit relevant clinical images to an appropriate database to enhance the value of the proposed project? (Yes or No) [Single-click here to add text]

If yes, describe the type and number of clinical images:[Single-click here to add text]

Describe the work that would be required to prepare and submit these clinical images to a database:[Single-click here to add text]

Total expected number of patient cases for whom clinical images would be submitted:[Single-click here to add text]

Total expected number of clinical images that would be submitted:[Single-click here to add text]

22. Projected timeline after final approval of the proposal, including start and completion dates, as well as anticipated time required for the biospecimen bank to locate, prepare, and ship specimens:[Single-click here to add text]

**23. Budget**

Please provide a budget using the PHS 398 (form and instructions available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> ) and additional information as described under “Budget Preparation” in the Announcement above. For NCTN Group proposals, separate budget sections and justifications should indicate which costs would be paid to each NCTN Group component. The budget must NOT include costs covered by any NCTN or NCORP grant. Please note that funding for approved proposals will be provided via a contract mechanism, rather than a grant supplement. Proposal budgets should be prepared accordingly.

**Appendices**

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