Clinical Proteomics Tumor Analysis Consortium (CPTAC)
Biospecimen Core Resource

Draft Statement of Work

Statement of Objectives

A. Background

A.1. General

The overall objective of the Clinical Proteomic Tumor Analysis Consortium (CPTAC) is to improve our understanding of cancer biology by conducting proteogenomic analysis on selected cancer types (***anticipated up to10 cancer types, 200 cases each; see Tumor Types of Interest***) where unanswered questions remain about the molecular biology of the disease. This analysis will add a complementary layer of protein molecular biology that facilitates refinement of driver genes, enhances understanding of the pathogenesis through proteomic subtyping, and illuminates dynamic alterations in posttranslational modifications responsible for the dysregulation of cancer signaling networks and pathways.
The purpose of this project is to utilize a pipeline to collect, process, qualify, genomically characterize, and distribute biospecimens for CPTAC and to collect, analyze, review, store, and distribute the data associated with this research.
The project involves several components, including:

- Tissue Source Sites (TSS)
- Biospecimen Core Resource (BCR)
- Genome Characterization Center (GCC)
- Quality Management System (QMS)
- Comprehensive Data Resource (NCI-OTS CDR)
- Proteome Characterization Centers (PCC)
- Proteo-Genomic Data Analysis Centers (PGDAC)
- Proteogenomic Translational Centers (PTC)
- Data Coordinating Center (DCC)

The pipeline of these components will supply high-quality biospecimens and data to a network of Proteome Characterization Centers (PCC), Proteogenomic Translational Centers (PTC), and Proteogenomic Data Analysis Centers (PGDAC). Ultimately, the samples will be characterized for copy number variation, single nucleotide polymorphisms, DNA, RNA, and protein expression and mutation analysis. De-identified data will be made available through the CPTAC Data Coordinating Center and other NIH data resources. Overall quality for the entire project will be the responsibility of the QMS.

Tumor Types of Interest

1. **Thoracic: Non-Small Cell Lung Carcinoma (Lung Adenocarcinoma)**

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2. **Gastrointestinal: Pancreatic Ductal Adenocarcinoma (PDA)**

3. **CNS: Glioblastoma Multiforme (GBM)**
4. **Hematologic: Acute Myeloid Leukemia (AML)**
5. **Urologic: Clear Cell Renal Cell Carcinoma (ccRCC)**
6. **Head And Neck: Head And Neck Squamous Cell Carcinoma (HNSCC)**
7. **Skin: Cutaneous Melanoma**
8. **Soft Tissue: Sarcomas**
9. **Thoracic: Lung Squamous Cell Carcinoma (SQCC)**
10. **Gynecologic: Uterine Corpus Endometrial Carcinoma (UCEC)**

A.2. CPTAC Biospecimen Core Resource

A major prerequisite of the CPTAC Program will be the acquisition of high quality biospecimens. To meet this need, NCI is establishing a network of Tissue Source Sites (TSS) to provide high quality, clinically annotated biospecimens for submission to a centralized quality control and processing facility. The TSSs will be procuring tumor tissue, normal tissue (when feasible) and blood (plasma and buffy coat/packed red cells) from patient volunteers suffering from up to 10 tumor types. The BCR will be the primary interface between the CPTAC Program and the TSSs.

It must be noted that the term “high quality” refers not only to the histological and molecular properties of the tissue, but also to characteristics such as degree and quality of clinical annotation, the existence of appropriate informed consent provisions for the intended use of the biomolecules and data, collection and subsequent distribution to CPTAC participants under an Institutional Review Board (IRB) approved protocol, as well as unencumbered access for research use (e.g., intellectual property restrictions).

CPTAC project management chose to establish a centralized tissue processing model to standardize procedures such as histopathology, DNA/RNA isolation, sequencing, and other sample preparation processes. This centralization specifically means that all operations to process tissue for any single cancer studied by CPTAC occur at the BCR, utilizing SOPs. This standardization refers to the processes of biospecimen receipt, logistical and physical management, processing into analytes (the molecular extracts from tissue such as DNA and RNA), the subdivision of tissue or analytes, and dissemination to the research sites with rigorous QC of all intermediate and final products along the workflow.

The BCR will work closely with the Comprehensive Data Resource (NCI-OTS CDR), which will manage biospecimen and clinical data, including sample identifiers.

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B. Objectives

The objective of this SOW is to establish a core resource providing comprehensive logistical support for the CPTAC Program facilitating tissue sample and clinical data collection, histopathological analysis, storage, and internal dissemination. It is envisioned that the contractor will put in place a seamless pipeline for accepting clinical samples and associated data, analyzing frozen-section slides (or images) for pathological analyses, storing the samples and data, preparing DNA and RNA from the samples, distributing the tissue samples to the PCCs and the DNA/RNA to the GCC, and conveying the clinical and sample data to the NCI-OTS CDR. It is further envisioned that the BCR will employ rigorous quality control and assurance practices for all aspects of the work in collaboration with the QMS. Finally, it is envisioned the BCR shall actively engage in routine communication regarding all aspects of the work with the CPTAC leadership and the other components of CPTAC.

C. Scope

The Contractor shall function as a fundamental resource and play a central logistical role in the CPTAC Program. Key elements of the scope shall include:

1. Coordinating the procurement of biospecimen collection and shipping from the CPTAC TSSs,
2. Coordinating clinical data procurement and transmission from the CPTAC TSSs,
3. Storing and managing the CPTAC biospecimen collection,
4. Managing and storing the CPTAC clinical data associated with the biospecimens,
5. Processing biospecimens for pathology review,
6. Processing the biospecimens for DNA and RNA,
7. Distributing biospecimens and analytes to the PCCs and GCC,
8. Coordinating with and distributing clinical and biospecimen data to the NCI-OTS CDR,
9. With the QMS, developing and implementing comprehensive quality control and assurance regimens for all aspects of the work,
10. Managing the operations of the BCR.

The Contractor shall be able to perform as a single entity all the biospecimen and data processing capabilities described in this SOW. Currently, the goal of the program is to accumulate 200 qualified tissues from each of up to cancer types. The Program estimates a qualification rate of 60% with a total of 333 consented patients enrolled in each of the eight tumor studies. Tissues shall be received by the Contractor from contributing CPTAC Tissue Source Sites (TSSs) that will be vetted by the NCI to meet a set of preliminary evaluation criteria. To account for the more rigorous tissue collection protocols needed for proteomic analyses, the tissue procurement will be prospective in all cases.

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D. Tasks

The objectives of the work will be realized through the following tasks and subtasks. Where needed, CPTAC requirements for the Contractor executing on the tasks and subtasks are noted in Section E. Many of the subtasks require direct communication between the CPTAC BCR and other components of the CPTAC Program. These communications will be done through or facilitated by the Contracting Officer's Representative (COR).

D.1. Task 1 - Coordinating the Procurement of Biospecimen Collection and Shipping from the CPTAC TSSs

D.1.a. Subtask 1.1 – Confirming that all regulatory and patient safety/confidentiality have been satisfied by the TSSs.

The contractor shall confirm that each TSS has obtained all needed, local approvals to perform the work and completed all the needed regulatory documents that are needed (e.g., Material Transfer Agreement (MTAs), etc.). Electronic copies of all documents will be made available through an electronic document storage system provided and hosted by a third party and available to the NCI COR.

D.1.b. Subtask 1.2 – Shipping of Biospecimens from the TSSs

The contractor shall provide for the shipping of biospecimens from the TSSs to the BCR including providing appropriate ultra-cold shippers that have temperature monitors. The contractor shall make the arrangements for shipping and pay for the costs. The contractor shall ensure that all specimens are tracked during shipping and relevant shipping parameters (e.g., temperature) collected and stored.

D.2. Task 2 - Coordinating Clinical Data Procurement and Transmission from the CPTAC TSSs

D.2.a. Subtask 2.1 – Providing an Electronic Clinical Data Submission Application

The Contractor shall put in place and administer a secure, electronic clinical-data management system that is capable of direct, internet-based access by the TSSs for the entry of clinical data.

D.2.b. Subtask 2.2 – Creating CPTAC-specific Clinical Case Report Forms

The contractor shall interact with the NCI Cobrand the CPTAC Program to create Program-specific clinical case report forms (CRF) and integrate these into the clinical data system from Subtask 2.1.

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D.2.c. Subtask 2.3 - Clinical Data Review

The contractor shall review clinical data submitted by the TSS on a timely basis to ensure completeness and internal consistency of the data.

D.3. Task 3 - Storing and Managing the CPTAC Biospecimen Collection

D.3.a. Subtask 3.1 – Cryostorage of CPTAC Samples and Analytes

The vendor shall provide comprehensive biobanking facilities for the long-term cryostorage of the CPTAC samples and derived analytes (vapor-phase liquid nitrogen).

D.3.b. Subtask 3.2 - Sample and Analyte Tracking

The contractor shall put in place and administer a secure, electronic sample tracking and laboratory information management system (LIMS) and utilize that system to track all CPTAC samples and analytes in its possession.

D.4. Task 4 – Storing and Managing the CPTAC Clinical and Biospecimen Data

D.4.a. Subtask 4.1 – Electronic Storing of CPTAC Clinical Data

The contractor shall put in place and administer a secure, computerized clinical data storage system with an external interface that can be made available to the TSSs and other stakeholders not on the contractor's site.

D.4.b. Subtask 4.2 - Electronic Storing of CPTAC Biospecimen Data and Tracking of Biospecimen Logistics

The Contractor shall put in place and administer a secure, computerized system for storing CPTAC Biospecimen data and tracking the logistics of biospecimen storage, handling, and shipping.

D.4.c. Subtask 4.3 – Providing UUIDs

The Contractor shall put in place and administer a computerized system for generating UUIDs.

D.4.d. Subtask 4.4 – Providing Comprehensive Electronic Data Storage for All CPTAC Data

The Contractor shall identify any additional software systems that may be needed to ensure that all relevant CPTAC data (e.g., electronic histopathology images) are securely stored in electronic format. Any additional systems shall be itemized in the

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Contractor's initial proposal or brought to the attention of the NCI COR during the Period of Performance. The Contractor shall be prepared to host and manage these systems if approved by the NCI COR.

Note that an exception to this is an electronic document inventory and storage system (e.g., SharePoint). A document storage and management system will be hosted by a third party and supplied to the Contractor.

D.4.e. Subtask 4.5 – Providing IT Security

The Contractor shall develop and implement the needed administrative processes and policies to provide security for the information systems holding CPTAC data and information.

D.5. Task 5 - Processing Biospecimens for Pathology Review

D.5.a. Subtask 5.1 – Preparing Frozen Histopathology Sections of CPTAC Samples

For all cases, the contractor shall create and securely store electronic images of the stained slides of representative frozen sections. TSSs will submit either slides or images to the BCR.

D.5.b. Subtask 5.2 – Pathologic Review of the Frozen Sections for Qualification

The Contractor shall provide for the analysis of the frozen sections received at the CPTAC BCR. The pathologic review of these sections shall include quantifying the percent of tumor nuclear profiles, the percent of necrosis in the section, and the total cellularity of the sample. In addition, the contractor shall coordinate with the TSSs for the acquisition of diagnostic histopathology slides on each case submitted by the TSSs.

D.5.c. Subtask 5.3 – Managing the Pathology Review Data

Along with the NCI-OTS CDR and QMS, the contractor shall develop processes and an electronic system for managing the pathology data obtained from the frozen sections. The contractor shall also develop an archival system for the electronic images and physical slides that are part of this effort.

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D.6. Task 6 - Processing the Biospecimens for DNA and RNA

D.6.a. Subtask 6.1 – DNA and RNA Isolation

The contractors shall use contemporary biomolecular techniques to isolate and purify DNA and RNA from representative solid tissue samples and blood from each qualified case.

D.6.b. Subtask 6.2 – Analyte Storage and Tracking

The contractor shall store the analytes under suitable conditions and track the analytes pending shipment to the GCC. The contractor shall utilize an internal IT system for tracking.

D.6.c Subtask 6.3 – Processing the Biospecimens for Protein

Because protein extraction is performed by each PCC, the BCR will not isolate protein material. When OCT is present, the BCR will remove OCT prior to preparing a sample for proteomic analysis. To ensure the homogeneity between the sample portion undergoing genomic analysis and the portion undergoing proteomic analysis, the BCR shall have the capability to conduct a variety of sample processing methods, including, but not limited to: serial slicing, cryopulverization, and laser-capture microdissection.

D.7. Task 7 - Distributing Biospecimens and Analytes to the PCCs and GCC

D.7.a. Subtask 7.1 – Distributing Biospecimens to the Protein Characterization Centers

The contractor shall coordinate with the CPTAC Steering Committee and NCI COR and distribute tumor samples to the PCCs and/or PTCs. The samples will be shipped frozen in cryo-shippers.

D.7.b. Subtask 7.2 – Distributing Analytes to the Genome Characterization Center

The contractor shall coordinate with the GCC and ship the DNA and RNA analytes.

D.8. Task 8 - Coordinating with and Distributing Clinical Data to the NCI-OTS CDR

D.8.a. Subtask.8.1 – Developing Data Transmission Procedures with the CPTAC NCI-OTS CDR.

The contractor shall interact with the CTPAC NCI-OTS CDR to develop the technological approach for transmitting the CPTAC clinical data to the NCI-OTS CDR.

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D.8.b. Subtask 8.2 – Distributing the CPTAC Clinical Data to the DCC

The contractor will electronically transfer the clinical data to the NCI-OTS CDR on a routine schedule. The schedule will be determined in consultation amongst the Contractor, CPTAC NCI-OTS CDR, and NCI COR.

D.9. Task 9 - Developing and Implementing Quality Control and Assurance Regimens for the Preparation of DNA and RNA

The contractor shall develop, implement, and use a comprehensive QC/QA regimen for the preparation of the molecular analytes and biospecimens. The results of the regimen shall be regularly reviewed by BCR management and the QMS and any systemic issues addressed.

D.10. Task 10 - Managing the Operations of the BCR

D.10.a. Subtask 10.1 – Document Management

The contractor shall manage all documents relating to the operations of the BCR. Note that an electronic document storage system hosted and managed by a third party will be provided for the Contractor.

D.10.b. Subtask 10.2 – Preparing Routine Biospecimen Inventory and Status Summaries

The Contractor shall prepare weekly inventory summaries of the inventory of the biospecimens that includes progress in each case towards qualification. The summaries shall be suitable for distribution to the CPTAC Program Staff, other CPTAC entities, and CPTAC community in general.

D.10.c. Subtask 10.3 – Preparing Standard Operating Procedures

In consultation with the NCI COR, CPTAC Program Staff and the QMS, the contractor shall identify key, recurring procedures and processes in the BCR and create, maintain, and update SOPs covering these activities.

D.10.d. Subtask 10.4 – Preparing Monthly Status Reports

The contractor shall create monthly status reports covering all aspects of the operation of the BCR including financials.

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D.10.e. Subtask 10.5 Project Close Out Plan

The contractor shall prepare a plan for project close out that describes the steps the Contractor believes would be necessary for relocating the physical sample collection and downloading the electronic information stored at the BCR.

D.10.f. Subtask 10.6 Communication Plans

This Contractor shall prepare Communication Plans for guiding interactions between or amongst the BCR and the CPTAC TSSs, CPTAC GCC, CPTAC NCI-OTS CDR, CPTAC QMS, CPTAC DCC, and CPTAC PCCs.

E. Requirements

The following sections contain additional details that apply to the specific tasks noted above. The information is organized to generally follow the major Task number.

E.1. Coordinating the Procurement of Biospecimen Collection and Shipping from the CPTAC TSSs

The Contractor shall have sufficient expertise and be of sufficient scale to support the procurement of biospecimens from ~50 TSSs to meet the overall biospecimen needs of the Program. Specific case and sample inclusion criteria are noted in the CPTAC Tissue Procurement Protocols. TSS interactions shall include the following activities as necessary to ensure that samples are collected, handled, shipped and received with full maintenance of quality:

a. Develop and deploy a TSS communication protocol that governs the Contractor's communications with the TSS, NCI, and potentially other organizations as needed to perform the work.
b. Develop and deploy a support system in which the BCR works directly with the TSSs to rapidly analyze, understand, and correct any tissue sample quality issues involving the TSSs that arise.
c. Develop and deploy a system for general support of the TSSs capable of rapid responses during normal working hours for the BCR and provisions for addressing issues that arise after normal working hours on the next business day.
d. Conduct biospecimen and data transfer training of TSS operators or other staff who shall physically collect and handle tissues and clinical data.
e. Travel to TSSs for onsite training may be conducted after approval by the NCI COR. Travel for two or more BCR staff may be approved if required for training of new TSS staff.

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f. Conduct a regular meeting (at least monthly) with the TSSs to determine TSS administrative status, sample and data review and retrieval status, and plans for future shipments to the BCR. It is envisioned this will minimally take the form of a teleconference hosted by the NCI COR with each TSS, NCI CPTAC Program personnel, the, and other relevant CPTAC personnel. If needed, routine one-on-one meetings with individual TSSs may be arranged through the NCI COR.

The Contractor shall execute MTAs with each TSS for transfer of biospecimens. The NCI will provide draft MTA documents including a Cover Memo specifying the minimum requirements and NIH policy stipulations for the MTA. The MTA may be modified during negotiations providing that the enumerated key requirements and policies in the Cover Memo are maintained as part of the terms. The Contractor shall seek guidance and authorization from the NCI COR prior to agreeing to any significant changes in MTA terms. The MTA and terms therein, while required under this contract, is a standalone legal agreement between the Contractor and the TSS; NCI is not a party to this MTA.

The Contractor shall obtain from contributing TSSs the necessary human subjects documentation verifying that TSS has received IRB approval to participate in CPTAC. Such documented approval may include:

a. An IRB approved protocol. In this case, an illustrative copy of the Informed Consent, the protocol, and the approval letter from the IRB must be provided.
b. A CPTAC-specific IRB waiver has been granted.
c. A CPTAC-specific letter that the IRB considers one of the exemptions in 45CFR46 applicable.
d. A CPTAC-specific letter that the IRB does not consider the use of these data and materials to be human subject's research.
e. Consent withdrawal process.

Once the BCR has established that a TSS has submitted appropriate regulatory documentation in good form, the BCR shall notify the TSS and the NCI CORs overseeing the TSS and the BCR that they may begin procuring tissue.

The Contractor shall retain copies of the annual review and re-approval of the aforementioned human subject's documentation. Copies of such documentation shall be stored by the Contractor and made available for inspection by NCI COR, NCI CPTAC Program Office, and to CPTAC network entities as designated by the NCI COR.

The Contractor shall coordinate and provide training as necessary with designated TSS to ensure that biospecimens are packed appropriately to protect them from loss, damage, and temperature variations during transit. The Contractor shall use vapor phase liquid nitrogen containers to receive frozen biospecimens. The shipping and handling of

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biospecimens shall meet relevant government regulations for packaging, labeling and shipping of such samples. Air shipments shall conform to the International Air Transport Association (IATA) standards; ground shipments in the United States shall conform to the Department of Transportation (DOT) standards.

Once the TSS regulatory and training requirements have been met, but prior to sending cryoports and authorizing shipments, the "Submission" and "Baseline" forms required of the TSSs shall be reviewed for completeness by the BCR and discrepancies addressed by the TSS. The TSSs will be required to create a shipping manifest for each shipment. The Contractor shall use the completed "Submission" form as a trigger to create a new TCGA case for that procurement. The Contractor shall develop and maintain a system for creating a unique CPTAC identifier that is independent of any more global system such as the Universally Unique Identifier (UUID) system noted below and assign and track a unique case identifier (see Section E.2.c below). The TSSs shall use that identifier for all activities surrounding that case. The Contractor shall assume that 600 shipments will be required during the Period of Performance.

Upon receipt, samples shall be immediately inspected to ensure integrity after shipping and consistency with the shipping manifest. Irregularities in sample quality or quantity shall be immediately communicated to the TSS and the NCI COR via email per the TSS communication plan required above. This electronic confirmation should be received within 24 hours of arrival of shipment at the BCR, excluding weekends and holidays. For example, if a shipment is received at 5pm on a Friday afternoon, the TSS will be notified no later than Monday at 5pm unless Monday is a holiday (in which case the site would be notified no later than Tuesday at 5pm). Any shipment that arrives compromised (e.g., evidence of melting) and that fails quality control prior to entry into the BCR LIMS will be handled according to the shipment receipt SOP.

Biospecimens shall be uniquely identified and tagged by the Contractor with machine readable mechanisms (e.g., UUID, barcodes, RFID) upon receipt and registered into an electronic inventory tracking system. The primary identifier will be the UUID, but additional IDs can be human-readable IDs. The Contractor shall be responsible for generating the IDs.

The Contractor shall provide the TSSs pre-labeled and pre-weighed cryovials suitable for the tumor and normal tissue types expected from the TSS. The goal is to minimize tissue handling at the TSSs. Tissue weights will be obtained at the BCR. All frozen sections will be prepared by the TSSs. The TSSs will be submitting multiple pieces (sub-sections) of tissue (up to five) obtained from each tumor. These pieces will be accessioned and treated as separate samples associated with a case. It is possible that situations will arise where the BCR receives multiple samples obtained from multiple independent tumors

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found in the same participant; the identification system should be able to account for this scenario.

E.2. Coordinating Clinical Data Procurement and Transmission from the CPTAC TSSs

E.2.a. Subject and Sample Information

The Contractor shall have the expertise and systems to receive and manage, at a minimum, the following information provided by the TSSs and associated with each case:

1. The CPTAC case Submission form (submitted electronically by the TSS)
2. The CPTAC case Baseline Case Report Form (submitted electronically by the TSS)
3. The surgical pathology report, in original source format modified by the TSS to meet de-identification requirements. This document shall be scanned and stored in the electronic record system if received as paper.
4. Scanned images of representative histopathology slides generated at the TSS. If needed, the Contractor may also be asked to accept physical slides from the TSS for imaging at the BCR and return the original slides to the TSS. If slides are submitted in lieu of images, they shall be scanned with a whole slide scanning system at an appropriate resolution to allow a pathological review. All image data shall be captured and annotated electronically. The Contractor shall ensure that an appropriate MTA has been executed.
5. The CPTAC One-Year Follow Up form

It is envisioned that the CPTAC Program will support following the patients providing tissue for up to five years. Only the one year follow up is within the scope of this SOW.

For histopathology images received from the TSSs, the BCR shall ensure that they are accompanied by appropriate data regarding magnification, etc. These data must be stored electronically in the Contractor's information systems associated with the images. If necessary, the BCR shall transform the data to meet the BCR's data standards.

E.2.b. Case Report Forms, Clinical Data Elements, Data Models, and Electronic Information Systems

The CPTAC Program has developed a set of case report forms (CRFs) specific for each cancer type to be studied. These include:

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1. Submission – Contains minimal information on the consented participant from which tissues are obtained. Completion and submission of this CRF by the TSS will be required at the time or surgery to provide the CPTAC Program with information regarding the inventory of samples at the TSS awaiting shipment to the BCR. The TSS must submit this information before shipping is scheduled.
2. Baseline – Contains relevant clinical information and diagnostic data on the consented participant from which tissues were obtained. Completion and submission of this CRF by the TSS will be required before shipping is scheduled.
3. One-Year Follow Up – Contains status and relevant clinical information on the participant one year after tissue procurement.

From time-to-time, other CRFs may need to be developed or the contents of the existing CRFs modified. The contractor shall work with the CPTAC Program Office, relevant CPTAC Working Groups, and the NCI COR to develop the contents of these forms. If changes are required, the Contractor shall track the changes over time and assist the DCC in updating cases that may have been uploaded prior to the changes.

The contractor shall review these forms and develop the corresponding Clinical Data Elements (CDEs) corresponding to the contents of the form. The term "clinical data elements" means all the patient data associated with biospecimens as required to be collected under this work, including, but not necessarily limited too, demography, pathology reports, other clinical history and data, and follow-up/outcomes data. Data elements may be provided to the Contractor in list, paper case report form, various electronic formats, or other formats not necessarily compliant with Informatics requirements of this SOW. The Contractor shall be responsible for conversion of such clinical data collection specifications into formats compliant with NCI standards as stated in Section E.4 of this SOW.

The CRFs will utilize common data elements in the NCI caDSR system (https://wiki.nci.nih.gov/display/caDSR/caDSR+Wiki+Home+Page). New CDEs will be created as required and submitted to the caDSR. Any modifications needed to existing CDEs will be submitted to the caDSR system.

With the exception of the pathology report, the collection of the clinical data shall be by direct electronic input into the BCR systems by computer-based input (i.e., electronic case report forms) systems, utilizing a software system capable of being deployed to the TSS via the internet and using web-based interfaces. The contractor shall securely host and maintain the electronic system. It is envisioned that the primary mechanism for the TSSs to submit data will be through the internet-based system although situations may arise from time-to-time where the BCR may need to

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manually enter data from paper-based forms or other media. Data submission by methods other than the selected web-based system will require the TSS to obtain approval by the NCI COR. It is not expected that additional electronic methods for the direct entry of data from the TSSs into the information system will be employed.

It is not currently envisioned that any of the contents of the pathology reports submitted to the BCR from the TSS will be extracted and stored in the BCR's clinical data repository.

If not already present, patient clinical data shall be augmented to include International Classification of Disease (ICD) codes for diagnosis and morphology, ICD-10 and ICD-O-3, respectively. The current latest approved ICD version shall be used. These data elements shall be part of the upload to DCC.

E.2.c. Protection of Human Subjects Related to Receipt of Tissues and Data

The Contractor shall be the custodian of data and samples received from patients enrolled as research subjects in IRB approved protocols at TSSs. The Contractor shall establish all the necessary policies, systems, and technologies to ensure patient protection as specified by regulation (e.g., HIPAA and the Common Rule), NIH policies covering CPTAC, and all related terms and conditions included in the subcontract. The Contractor shall serve as the interface between the TSSs, which work with fully identified patient data and the CPTAC DCC database, which shall only have access to linked patient data that are stripped of direct identifiers.

Specific requirement(s) for patient protection include:

1. The Contractor shall not use the biospecimens or data to support its own research.
2. The Contractor shall conform to all relevant human subjects and privacy regulations under HIPAA, 45CFR46, and any relevant state and local regulations. Note that FDA regulations (e.g., CFR Title 21) do not apply to this project.
3. The Contractor shall abide by requirements in the IRB approved protocols under which the samples and data were originally collected and of which the Contractor is made aware by TSSs.
4. The Contractor may receive clinical data that are considered Protected Health Information (PHI) according to HIPAA; however, that data shall be provided by the source site in a form suitable to meet the "Limited Data Set" (LDS) requirements under the regulations. The Contractor shall deploy a QC process to ensure that data meet the "Limited Data Set" specification. The Contractor shall enter into HIPAA described "Data Use Agreements" with contributing sites.

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The "Data Use Agreement" language is already part of the MTA document template that shall be provided by the NCI.

5. The Contractor shall be able to operate with, and internally manage, PHI clinical data compliant with the HIPAA "Limited Data Set" specification.
6. The Contractor shall submit its clinical data HIPAA compliance testing plan to NCI upon subcontract execution, to ensure that received data meet the HIPAA LDS specification, and do not include direct identifiers.
7. The Contractor shall have systems in place to effectively de-identify those data to be HIPAA "Safe Harbor" De-Identified compliant to support access of data by any external entity that does not have a HIPAA compliant "Data use agreement" in place with the Contractor. Only HIPAA De-Identified compliant data will be distributed with tissues or molecular analytes to other CPTAC participants.
8. The Contractor may receive and histopathologically review a biospecimen and find a discrepancy between its finding and the TSS diagnosis of clinical relevance to the patient. The Contractor shall have an SOP in place to address this eventuality. The SOP shall include at least the following features:
    a. Plan for verifying the discrepancy to the greatest degree possible with internal (Contractor held) information.
    b. Processes for communication back to TSS PI or TSS IRB, if necessary.
    c. Decision tree for whether such samples can be used by CPTAC at the end of the discrepancy resolution process.
9. The Contractor shall work with two (2) types of coded patient identifiers. TSS shall provide BCR samples and data that are coded with a TSS ID (the linkage database between a Patient ID and the TSS ID shall be maintained at each TSS). The Contractor shall further de-reference the TSS ID by associating it to an information-free CPTAC UUID generated by the Contractor. The linkage database between the TSS ID and CPTAC primary ID shall be maintained by the Contractor. All management, processing and distribution of samples, derivatives and data by the Contractor shall use the CPTAC primary ID. Third party access to the Contractor linkage database shall only be granted upon written approval by the NCI COR per the requirements stated in CPTAC Patient Protection and Data Access policies, or by approval of the TSS Principal Investigator (PI).
10. The Contractor shall receive its own IRB approval, in the form of a waiver, exemption or other documentation, to perform the work in this SOW, and provide such documentation to the NCI COR and NCI CPTAC Program Office.

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11. The Contractor shall be responsible for determining that a TSS, and the samples and data it ships to the Contractor, are done so in accordance with the human subjects protection requirements under which the Contractor shall operate. Specifically, the Contractor shall be responsible for making the decision that all human subjects' requirements have been met before receiving samples and data. These requirements are those placed upon the Contractor by this SOW and by its own IRB approvals. Note, NCI may receive and review various TSS human subjects documentation, including informed consents, protocols, and IRB approvals, and shall provide such documentation to the Contractor when available; however, is not responsible for making the determination that human subjects requirements have been met.
12. The Contractor shall abide by NIH (including NCI and NHGRI) patient and data protection policies established for CPTAC.
13. The Contractor shall have an SOP governing the withdrawal of a participant from CPTAC. Notification of such withdrawal will come from the TSS. The SOP shall include suitable notification mechanisms to the DCC.
14. The Contractor shall obtain an NIH Certificate of Confidentiality (http://grants1.nih.gov/grants/policy/coc/appl_extramural.htm) to cover itself and the TSS providing samples to it within upon contract initiation.

E.2.d. Clinical Data Review

Data shall be Quality Controlled to meet interim quality checks "sanity checks" upon input into the Contractor's systems. Interim quality checks shall include, at a minimum:

1. Date sequences and continuity are reasonable.
2. Values are within permitted value domain lists, numerical range, and appropriate units.
3. Data submitted through the electronic system corresponds to information provided in the pathology reports and histopathology images submitted by the TSS.
4. All TSS submitted data conform to the histopathology of the frozen sections obtained at the BCR.

E.3. Storing and Managing the CPTAC Biospecimen Collection

Biospecimen Management encompasses the logistics of biospecimen collections and receipt, annotation, storage management, location management, internal movement and distribution. To achieve this function, the Contractor shall obtain or develop SOPs for all

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processes involved in tissue sample collection, receipt, storage, and distribution. The sample management function shall employ an informatics infrastructure to support workflow, and ensure complete logging of all sample access and sample movement transactions.

E.3.a. Specific Requirements for Biospecimen Storage

E.3.a.(1). The Contractor shall support the following storage environments:

a. Vapor phase liquid nitrogen freezers (-186°C to -150°C).
b. -80°C and -20°C mechanical freezers.
c. Humidity and room temperature controlled areas.

E.3.a.(2). The Contractor shall support repositories for:

a. FFPE slides.
b. Frozen tissue cryo-vials.
c. Blood and blood components in liquid and pellet form.
d. DNA, RNA.

E.3.a.(3). The Contractor shall be able to store long-term, per tumor project:

a. 2000 total solid tissues in individual cryotubes in at -150°C. This number represents 333 cases with 5 tumor sub-samples and 1 normal sample in an individual cryotube per case.
b. 333 buffy coat preparations at -150°C.
c. Up to ten 96 well plates of mRNA for RNA-SEQ at -150°C.
d. Up to ten 96 well plates of mRNA for miRNA-SEQ at -150°C.
e. Up to ten 96 well plates of tumor DNA at -150°C.
f. Up to ten 96 well plates of normal DNA at -150°C.
g. Up to 1500 2D Data Matrix tubes (bottom and side labeled), stored according the analyte within.
h. Up to 3000 FFPE slides at room temperature
i. Up to 3000 frozen-section slides at room temperature

E.3.a.(4). Additional Requirements for Biospecimen Storage.

a. Additional working storage space in the above environments to support the internal operations of the BCR for activities such as processing, QC, backup, and working storage prior to shipment of analytes.
b. All biospecimens shall be stored according to best practices (and under the control of specific SOPs), including continuous temperature monitoring, systematic equipment maintenance, emergency preparedness, alarm

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systems, back-up storage capacity, back-up liquid nitrogen supply and back-up power supply. The Contractor shall have a protocol for personnel notification and action in the event of emergency.

c. Tissue biospecimens that are stored at liquid nitrogen vapor temperature shall be managed according to SOPs that minimize warming.

d. Before any personnel start work on this contract, each individual needs to have proper training to perform all tasks as described in SOPs. The BCR will be required to perform regular documented training of study personnel. The BCR shall provide documentation of this required training in their monthly report to ensure that all staff is appropriately prepared to undertake the assigned work.

E.3.b. Each step of biospecimen logistics for all samples shall be supported and data collected in computer systems capable of exporting data according to the requirements to be developed for transmitting data to the CPTAC DCC (Section E.8) A high throughput, production ready software system to support the logistics shall be required.

E.4. Managing and Storing the CPTAC Data

The Contractor's electronic systems shall support collection, management and distribution of all data described in this SOW in a secure and well-described informatics environment. This includes managing and storing the biological data associated with the biospecimens such as the clinical and biospecimen data obtained from the TSSs as well as biospecimen annotation data developed at the BCR (e.g., pathology annotation and specimen-specific characterizations). Additionally, these systems shall support logistical and laboratory processes as described elsewhere in the SOW, and collect relevant tracking and QC data. The Contractor shall interact with the CPTAC DCC and CPTAC NCI-OTS CDR as necessary to ensure that data conform to CPTAC Project requirements, NIH policy, are appropriately accessible and capable of integration with the molecular and proteomic data. The CPTAC DCC shall be the ultimate repository of all outwardly accessible data generated as part of the CPTAC Project (see https://cptac-data-portal.georgetown.edu/cptacPublic/). The creation of a CPTAC-wide database by the Contractor is not in the scope of this SOW. The Contractor's informatics responsibility is limited to biospecimen associated data including, but not necessarily limited to: TSS information and protocols, clinical data, pathology data, histological and molecular processing and QC and annotation, and biospecimen and molecular analyte tracking.

Syntactic and semantic interoperability of the data collected throughout the entire CPTAC program is a requirement for the project. The Contractor shall ensure that the data delivered from its informatics systems to the CPTAC DCC are compliant with NCI

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compatibility guidelines for creating the Common Data Elements (CDE) that make up the CRFs. (https://wiki.nci.nih.gov/display/caDSR/caDSR+Wiki+Home+Page). The Contractor shall be given points of contact by the NCI COR in the NCI CBIIT that shall provide guidance and assistance.

Note that the requirements listed below describe functionality expected across the entire IT infrastructure of the BCR and not intended to describe the characteristics or specific functionality of any single IT solution or software suite used to create the infrastructure. The Contractor shall ensure that their overall informatics system is capable of meeting the requirements while providing the capability of efficiently extracting the information for transmission to the CPTAC DCC and creating reports and dashboards.

E.4.a. Specific Requirements for the Electronic Storage of CPTAC Clinical Data

The Contractor shall securely deploy and maintain an informatics system that shall collect, store, and distribute biospecimen and clinical data from TSSs and any additional data generated at the BCR that is most appropriately stored in the clinical system. The Contractor shall be aware that data elements and data models may change during the Period of Performance, but any changes do not diminish the requirements to have this system deployed and continually operational. Data associated with the patient cases and their biospecimens that shall be managed include, but are not necessarily limited to:

1. Allowable use, as obtained from the informed consent and IRB protocol.
2. Contractual status, related to terms from MTAs and other IP restrictions relevant to BCR operations and use of biospecimens and data within CPTAC.
3. Biospecimen and associated clinical data received from TSS.
4. Histopathology data from either the TSS or developed internally.

The Contractor's clinical data storage system shall allow conformance with the patient protection requirements described in Section E.2.c. The Contractor's clinical data storage system shall also allow the creation of the electronic CRF described in Section E.2.c. and the secure, web-based access required by the TSS for data entry into the CRFs.

E.4.b. Specific Requirements for Biospecimen Computer-based Tracking: "Supply Chain" Logistics, Receipt and Shipment, and Storage

The Contractor shall develop and maintain live online electronic computer-based records for biospecimen receipt, processing, quality control, storage, management and distribution operations for incoming tissue and their nucleic acid extracts. The

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Contractor shall implement a bioinformatics Laboratory Informatics System (LIMS) which supports and logs all sample receipts, locations, accesses, movements, processes and modifications, process results, and distributions. The electronic recording system shall capture data at sufficient detail to be able to account for every non-transient biospecimen and derivative that is received or created for CPTAC. Data shall be captured at the level of individual samples and groups of samples. Minimally, "groups" includes collections of samples that represent samples received as a group, processed as various batches, and distributed as a batch. The system shall track sample transactions in sufficient detail to provide a complete audit trail. Such tracking shall include, but not necessarily be limited to:

1. Shipment from TSSs, receipt, initial biospecimen registration, and the results of quality review of specimens at receipt.
2. Intended CPTAC purpose of the case and the samples associated with it, as known at accession or later modified while under the Contractor's custody (e.g., is the sample for regular CPTAC data generation or part of a cancer-specific pilot project to test new protein extraction techniques, new tissue processing techniques, etc.).
3. Tissue sample accesses for pathology verification purposes, including biospecimen access and return to inventory, sections cut, and slides generated. This includes dates and time stamps for all transactions, and freeze-thaw cycles for OCT embedded tissues and other frozen biospecimens.
4. Freezer and storage unit accesses.
5. Processing of tissue samples into subcomponents or derivatives.
6. Processing step that includes sample warming above its normal storage temperature
7. Amount of sample distributed and to whom and when, along with tracking of residual quantities.
8. Sub-dividing of tissue samples (including macro- or micro-dissection of tissues).
9. Aliquotting of molecular derivatives.
10. Dilutions or concentrations of analytes.

All non-transient biospecimens shall be uniquely identified with one or more alpha-numeric strings (barcodes). In addition to any CPTAC and the Contractor's specific identifiers, see the requirements section on UUIDs for additional requirements on sample IDs.

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Barcodes (or other machine readable tags, such as RFID) shall be used for all sample identification. All samples and aliquots shall be uniquely identified electronically and as otherwise specified. Physical objects labeled or tagged with the machine-readable ID (e.g., barcode, RFID) shall also include a human readable component if necessary to support manual manipulations of that object. Labels shall be documented to adhere within all processing and storage environments.

The LIMS shall be linked to laboratory processing and analysis equipment used in production, and shall support automated upload of data from that instrumentation for any type of data reportable under this work.

E.4.c. CPTAC Universally Unique Identifier (UUID)

The Contractor shall ensure that all CPTAC business objects under its purview are universally and uniquely identified. All non-transient objects tracked in the BCR databases shall have a CPTAC UUID.

1. The Contractor is responsible for obtaining or developing a system to generate UUIDs.
2. The CPTAC UUID shall not necessarily supplant other identifiers currently used for regular operations, both human and machine, within CPTAC network.
3. The BCR shall implement software, data models, and other systems as necessary to be capable of:
    a. Generating UUID locally, for association with any object received not already associated with at CPTAC UUID.
    b. Receiving UUIDs, individually, within a range, or in batches, from other CPTAC entities to associate with not-yet-ID'd objects in its databases.
    c. Distributing the UUID as required with all data and sample distributions.
    d. Maintaining the UUID association in all databases and data distributions required under this statement of work.
4. As needed, the Contractor shall transmit UUIDs back to the TSSs.

E.4.d. Other System Requirements

1. The Contractor shall utilize an electronic system to collect, store and share all comparable tissue and molecular analyte Quality Control data collected from TSS and generated by the Contractor. These data shall include, but are not necessarily limited to:
    a. Results of the analyses of frozen sections.

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b. Contamination testing.
c. Laboratory processing steps hypothesized to affect quality.
d. DNA and RNA quality testing.

2. The overall system shall be capable of web-based, live access to all CPTAC information including the tissue inventory accessible to any authorized personnel such as the NCI COR, the NCI CPTAC Program Officer, their delegates, or others as requested by the NCI COR. Authorization levels and permissions shall be discussed and agreed upon with the NCI COR.
3. The ability to extract data, as specified throughout this SOW, from all relevant BCR/Contractor software systems, to be delivered to CPTAC DCC in accordance with the technical specifications to be developed (Section E.8).
4. The Contractor shall work in collaboration with the CPTAC DCC, CPTAC Program staff, NCI CBIIT, and the NCI COR to design and maintain the data transmission technical specifications. Technical specifications may undergo improvement over the course of the project. The Contractor shall maintain relevant clinical informatics capability to support such improvement.
5. All informatics systems required in this SOW must be fully operational upon execution of this contract, except where specifically noted.
6. Clinical data shall be captured in such a way that the contractor can report on data collection completeness and data collection progress at the cancer, CPTAC TSS, distribution batch, case and individual data element level. The Contractor shall report on status of data collection progress as part of regular reporting requirements.
7. The contractor shall prepare and maintain an IT system architecture and design document containing a detailed description of the system
8. The Contractor shall prepare and maintain documentation describing the processes for routine IT system maintenance and backup.

E.4.e. IT Security

The Contractor shall be responsible for properly protecting all CPTAC information gathered under this SOW. The Contractor shall establish and implement administrative, technical, and physical safeguards to ensure the security and confidentiality of the CPTAC data and information. The Contractor shall perform an IT risk assessment on their system and develop and then implement an approved IT security plan for the CPTAC data.

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E.4.e.(1). Contractor Responsibilities

The contractor is responsible for:

a. Protecting CPTAC information in order to ensure its:

   i. Integrity, which means guarding against improper information modification or destruction, and includes ensuring information non-repudiation and authenticity;

   ii. Confidentiality, which means preserving authorized restrictions on access and disclosure, including means for protecting personal privacy and proprietary information; and,

   iii. Availability, which means ensuring timely and reliable access to and use of information.

b. Providing security of any Contractor systems operated for the performance of the work in this SOW and CPTAC information contained therein.

c. Adopting, and implementing, at a minimum, the policies, procedures, controls, and standards of the HHS Information Security Program to ensure the integrity, confidentiality, and availability of CPTAC information and for which the Contractor is responsible under this subcontract or to which it may otherwise have access under this subcontract. The HHS Information Security Program is outlined in the HHS Information Security Program Policy, which is available on the HHS Office of the Chief Information Officer's (OCIO) Web site (http://www.hhs.gov/ocio/index.html).

E.4.e.(2). Security Deliverables

a. IT Risk Assessment: An IT Risk Assessment shall be performed that is consent with that found in NIST "Guide for Conducting Risk Assessments" (NIST Special Publication 800-30, Revision 1, http://csrc.nist.gov/publications/nistpubs/800-30-rev1/sp800_30_r1.pdf) and any additions or augmentations described in the HHS–OCIO Information Systems Security and Privacy Policy.

b. IT Security Plan: An IT Security Plan shall be developed that is consistent with that found in the NIST "Guide for Developing Security Plans for Federal Information Systems (NIST Special Publication 800-18, Rev 1, http://csrc.nist.gov/publications/nistpubs/800-18-Rev1/sp800-18-Rev1-final.pdf).

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In assessing the security of the system, the Contractor shall assume that the Integrity, Confidentiality, and Availability of the systems operated for this SOW containing CPTAC information and CPTAC information would each be categorized as "Moderate" as defined in the NIST Standard for Security Categorization of Federal Information and Information Systems (NIST FIPS PUB 199, http://csrc.nist.gov/publications/fips/fips199/FIPS-PUB-199-final.pdf).

E.5. Processing Biospecimens for Qualification

E.5.a. Preparing Frozen Histopathology Sections of CPTAC Samples

A major consideration for the CPTAC tissue procurement is to avoid the use of tissue specimens for proteomic analyses that have been embedded in OCT mounting medium. The TSSs will be submitting multiple, independent segments from the same tumor obtained in a case and these subsamples will NOT have been prescreened with frozen sections by the TSS submitting the case. The TSSs will be submitting a deidentified pathology report as part of shipping to ensure that the tumor staging determined by the TSS meets CPTAC inclusion criteria for the case. The BCR shall be responsible for obtaining frozen sections from each tumor segment to ensure that the histopathology of each segment is consistent with the submitted pathology report and that the segment meets the CPTAC cellular composition values.

The Contractor shall use the frozen sections to determine tissue and cancer specific cellular composition values that qualify or disqualify a segment for molecular processing. Tissue segments shall be annotated with these values in the information system and a derived usability status shall be added to the annotation. The default criteria are a minimum of 60% tumor nuclei and a maximum of 20% necrotic tissue composition. Any changes to these default "cut-off" values for any particular cancer shall be approved by CPTAC Program staff and communicated to the BCR by the NCI COR. Additional criteria may be added and changed by NCI during the course of the project based upon feedback from CPTAC management and investigators.

The Contractor shall prepare at least one slide from each tumor segment. The slide(s) shall be processed and stained with hematoxylin and eosin using standard techniques. The slide(s) (or images) shall be reviewed by a BCR general pathologist to determine if a sample passes this test are maintained in the Pathology Pre-Screen SOP. Additional requirements include:

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1. For tumor segments not meeting pre-screen pathology quality control metrics, that segment shall be considered disqualified and shall not move on into BCR production. The segments shall be stored at Contractor's site.
2. For any case where at least two tumor segments pass the pre-screen, that case will move into full BCR production with at least one segment provided to a PCC for proteomic analysis and the other segment utilized for genomic analysis.
3. The CPTAC Biospecimen Working Group may modify these criteria on a per-cancer basis, and, upon notification from the NCI COR, the Contractor has responsibility for updating the SOP, submitting it for approval, and then implementing new cut-off metrics.
4. The Contractor shall track all pre-screen cases and the corresponding subsamples in its database along with the results of the pre-screening process.
5. The Contractor shall provide pre-screen reports according to the reporting requirements elsewhere in this SOW.
6. The Contractor pre-screen SOPs shall be well integrated with the regular pathology QC operations and minimize sample handling and freeze-thaw cycles.
7. The Contractor shall prepare images of each slide and store those images in their IT system and that of the NCI-OTS CDR.

E.5.b. Coordinating External Review of the Histopathological Data

Over the Period of Performance, it is likely that CPTAC participants may want to review the histopathology of the samples included in proteomics analyses. It will be within the scope work for the BCR to accommodate and coordinate any review once approved by the NCI COR. These reviews may be desired or necessary to adjudicate borderline cases or to collect data elements not determinable except by a specialist.

In the event of a review, the Contractor shall be prepared to provide an approved reviewer or reviewers the following information in electronic format:

1. Images submitted by the TSS.
2. Images of frozen sections obtained by the BCR.
3. Deidentified pathology reports.
4. Clinical information contained within the BCR's IT systems.
5. Biospecimen information contained within the BCR's IT systems.

The data to be collected during a review shall be specified prior to the review and may vary per tumor type. If new CDEs are required, the Contractor shall work with the CPTAC Biospecimen Working Group, the CPTAC Program Office, the NCI COR, and the reviewer(s) to develop the additional electronic or physical forms required to accommodate the review and then store the additional information in their IT systems.

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In the event of a review, the contractor shall propose approaches that minimize unexpected resource requirements yet still meet the practical and informatics needs of this requirement.

E.6. Processing the Biospecimens for DNA and RNA

One objective of the CPTAC project is generating genomic data on the samples employed for proteomic analyses. An objective for the BCR is the generation of DNA and RNA derived from tumor samples and blood from the same patient for germline data. The genomic characterization for all solid tissue (tumor and nonmalignant) samples will include exome sequencing along with mRNA and miRNA identification and quantification by RNA-SEQ. The DNA extracted from blood will be used for germline analysis by exome sequencing. The Contractor shall be responsible for all biospecimen processing into DNA and RNA. All sample processing must be performed according to SOPs, with a full QA plan in place to permit auditing of performance and resulting molecular quality in accordance with the QMS. Each sample shall be tested as part of QC procedures to capture molecular characteristics relevant to the quality of analytes. QC data shall be captured electronically, and made available online via the inventory management system specified in the Informatics section.

E.6.a. DNA and RNA Isolation

The Contractor shall process biospecimens to derive, store, and analyze (for quality control purposes) DNA and RNA from resected, tumor and nomalignant tissues and whole blood. The Contractor shall store biospecimens as tissues, and initiate production of molecular analytes upon a schedule and batch size process to be determined with the CPTAC Program and the NCI COR. The Contractor shall be of sufficient scale to perform DNA and RNA isolations from tumor and DNA isolations from blood for 2667 total cases over the Period of Performance.

The Contractor shall implement SOPs for analyte preparation they propose to use together with supporting data on the resulting sample stability over time. The protocols actually implemented by the Contractor shall be approved by the NCI COR.

The Contractor shall use laboratory automation whenever possible to improve economy of scale

1. Laboratory automation may be utilized in molecular analyte isolation from tumor samples or blood, plating aliquots of molecular analytes for storage or distribution, creating dilution of molecular analytes and other automatable processes.

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2. If used, SOPs shall be specifically developed for automated laboratory procedures.
3. An automation team, distinct from production personnel, should be used to develop, validate and implement laboratory automation.
4. QA/QC tracking of automated processes is required. The QC results of all automated processes shall be electronically recorded in the LIMS and made available to the NCI COR and the CPTAC Program Office.

E.6.a.(1). Specific requirements – Tumor Tissue

Approval to isolate molecular analytes from tumor tissue is not required on a case by case basis. Samples shall enter production in batches. Batch content (i.e., the sample comprising a batch) shall be identified by the Contractor and designed to optimize production flow, also taking into account project needs. The samples that fail to meet QC criteria shall be evaluated on an individual basis and released for characterization at the discretion of the NCI COR.

The Contractor shall use the histopathology results developed through the local preparation and inspection of frozen sections to determine which specific cases and samples undergo processing into analytes. The contractor shall regularly report to the NCI COR on sample IDs, and the Processing Batch IDs within which the samples are grouped, entering processing.

When processing of a sample is initiated, sufficient tissue shall be processed to yield enough nucleic acid for the expected characterization centers receiving distributions from that sample. SOPs shall be optimized to attempt to retain as much of the sample as possible in the original tissue format. Only one tumor segment from each case will be processed into DNA and RNA. For cases were the first attempt at DNA and RNA isolation from a tumor segment totally fails, the Contractor shall consult with the NCI COR regarding an additional attempt.

The Contractor shall implement SOPs for the handling and processing of solid tissues for the purpose of co-isolating DNA and RNA. The Contractor shall minimize the warming of tissues above liquid nitrogen temperature and process tissue into molecular analyte at the same physical site at which the biospecimen is stored, specifically minimizing additional transit. After their preparation, all analytes and aliquots shall be stored according to the governing SOPs.

The Contractor shall use an appropriate molecular technology for co-isolation of DNA and RNA from the same tumor segment. Any modifications to the isolation protocol agreed upon on the initiation of the work will require prior approval by the NCI COR before implementation.

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DNA and RNA extraction from tumor tissues shall meet the following requirements:

a. A minimum 10% of the total RNA yield shall be drawn off and reserved for micro RNA analysis.
b. Nucleic acid may be aliquoted into 96 well polypropylene trays or data matrix tubes. The Contractor shall be prepared to do both, as the characterization centers vary in their ability and requirements to receive analytes in certain formats.
c. The DNA aliquots shall be dissolved, stored and aliquoted according to the governing SOPs.
d. The RNA aliquots shall be dissolved, stored and aliquoted according to the governing SOPs
e. The quality control steps (Section E.9) shall be performed and the data shall be electronically captured in the LIMS and organized by batches, TSS, cancer, plate content, and other key variables.

E.6.a.(2). Specific requirements – Peripheral Blood

Approval to isolate DNA from blood is not required on a case by case basis. Samples shall enter production in batches. Batch content (i.e., the sample comprising a batch) shall be identified by the Contractor and designed to optimize production flow, also taking into account project needs. The samples that fail to meet QC criteria shall be evaluated on an individual basis and released for characterization at the discretion of the NCI COR. The Contractor shall only process blood from cases where tumor samples where qualified and DNA and RNA was successfully isolated.

The Contractor shall use an appropriate molecular technology for isolated DNA from the blood (. Any modifications to the isolation protocol agreed upon on the initiation of the work will require prior approval by the NCI COR before implementation.

DNA extraction from germline-source tissues shall meet the following requirements:

a. All applicable details applicable to processing of nucleic acids from tumor tissue apply to processing of normal tissue.
b. The germline DNA aliquots shall be dissolved, stored and aliquoted according to the governing SOPs.
c. The quality control steps (Section E.9) shall be performed.

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E.7. Distributing Biospecimens and Analytes to the PCCs and GCC

E.7.a. Distributing Biospecimens to the Protein Characterization Centers

In general, the Contractor will ship all biospecimens of one tumor type to one PCC. This shipment may occur in multiple batches with 25 cases comprising the minimum batch. With the assistance of the NCI COR, the Contractor shall develop a communication plan with the PCCs that includes a mechanism by which the PCCs can readily ascertain the type and quantity of full qualified tumor and normal specimens that are available for shipping.

The Contractor shall execute MTAs with CPTAC PCCs that shall be receiving materials. NCI shall provide a cover memo describing NCI policies for CPTAC and a template MTA currently used within the project. The MTA addresses specimen and data ownerships issues, IP, patient privacy and confidentiality issues, and requires that researchers receiving biospecimens from the BCR shall not attempt to identify or re-contact donors, or their relatives. The Contractor shall provide TSS and BCR human subjects' documentation to the PCCs as requested to support the PCC PI submissions to local IRBs. Tissue distribution to investigators outside the CPTAC Project network will require specific written approval from the CPTAC Program Director and concurrence from the NCI COR.

Once the PCCs have established with the BCR that all local approvals are in place for receiving tissues and all agreements involving the BCR and PCCs have been executed, the Contractor shall provide requested biospecimens to the PCCs. It is possible that the BCR will be requested to pre-process the biospecimen to be shipped to the PCC for subsequent proteomic analysis. The Contractor shall be prepared to utilize the coVARIS cryoPREP™ (http://covarisinc.com/products/cryoprep-extraction/) system for this pre-processing. Other requested pre-processing methods may include serial slicing or laser-capture microdissection. Requests from the PCCs for this pre-processing will be approved by the NCI COR. If the request is made and approved, the Contractor shall perform the processing, annotate the biospecimen record in the LIMS accordingly, and ship the extract. A SOP will be developed in collaboration with the NCI COR, CPTAC Program Office, and an appropriate CPTAC Working Group. The SOP will be maintained by BCR.

The Contractor shall ship samples or extracts using appropriate ultra-cold shippers that have temperature monitors to the requesting PCCs. The contractor shall ensure that all specimens are tracked during shipping and relevant shipping parameters (e.g., temperature) collected and stored. The Subcontract shall pay the

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cost for shipping to the PCC and the costs of returning the shipper to the BCR. Over the Period of Performance, the Contractor shall assume that a total of 75 shipments to the PCCs will be required.

All distribution of biospecimens shall include manifests of the shipped material as well as manifests of associated data, including, but not necessarily limited to, specimen identifiers and quantity. Data shall be provided to both receiving site and DCC in formats to be specified. The shipment of biospecimens shall be recorded in the BCR electronic systems.

E.7.b. Distributing DNA and RNA to the Genome Characterization Center

It is currently envisioned that the Contractor shall distribute DNA and RNA to the GCC in 60 batches with a minimum batch size of 24 samples. The ideal batch size is 96 samples. The exact shipping frequencies and schedules will be determined when the GCC is established and communicated to the Contractor by the NCI COR. DNA and RNA distribution to investigators outside the CPTAC Project network will require specific written approval from the CPTAC Program Director and concurrence from the NCI COR.

The Contractor shall provide to the GCC isolated DNA and RNA from the tumor biospecimen, nonmalignant tissue biospecimen, and the blood biospecimen (DNA only).

The Contractor shall execute MTAs with the GCC that will be receiving materials when it is in place. NCI shall provide a cover memo describing NCI policies for CPTAC and a template MTA currently used within the project. The MTA addresses specimen and data ownerships issues, IP, patient privacy and confidentiality issues, and requires that researchers receiving analytes from the BCR shall not attempt to identify or re-contact donors, or their relatives. The Contractor shall provide TSS and BCR human subjects' documentation to the GCC as requested to support the GCC PI submissions to local IRBs.

Once the GCC has established with the BCR that all local approvals are in place for receiving DNA and RNA and all agreements involving the BCR and GCC have been executed, the Contractor shall provide requested analytes to the GCC. The Contractor shall ship samples using appropriate ultra-cold shippers that have temperature monitors. The Contractor shall pay the cost for shipping to the GCC and the costs of returning the shipper to the BCR. Over the Period of Performance, the Contractor shall assume that a total of 3 shipments to the GCC will be required.

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DNA and RNA aliquots shall be distributed at amounts and concentrations to be specified when the GCC is established. All distributions will be recorded in the LIMS, including recipient, dates, and specific analyte aliquot IDs, and amounts.

Once the GCC has established that all local approvals are in place for receiving tissues and all agreements involving the BCR and PCCs have been executed, the Contractor shall provide requested biospecimens to the PCCs. The Contractor shall ship samples using appropriate ultra-cold shippers that have temperature monitors to the requesting PCCs. The Subcontract shall pay the cost for shipping to the PCC and the costs of returning the shipper to the BCR. Over the Period of Performance, the Contractor shall assume that a total of 65 shipments to the PCCs will be required.

All distribution of DNA and RNA shall include manifests of the shipped material as well as manifests of associated data, including, but not necessarily limited to, specimen identifiers and receiving site, quantity, concentration, and certain QC data. Data shall be provided to both receiving site and DCC in formats to be specified. The QC results of biospecimen distributions shall be electronically recorded and made available to the GCC, CPTAC Program, and NCI COR. The shipment of biospecimens shall be recorded in the BCR electronic systems.

E.8. Coordinating with and Distributing CPTAC Data to the DCC

E.8.a. Developing Data Transmission Procedures with the CPTAC DCC

The contractor shall interact with the CPTAC DCR to identify the most efficient technical approach for transmitting the clinical case data and relevant sample data contained in the LIMS to the NCI-OTS CDR. The interactions will be coordinated by the NCI COR.

With the assistance of the NCI COR, the Contractor shall develop a communication plan with the NCI-OTS CDR that includes a mechanism to identify appropriate data format requirements and the specific mechanism for transmittal in a form that can be captured and acted upon by the Contractor. The Contractor shall be responsible for developing the SOP covering the final data format and transmission procedure. The final SOP will require the approval of the NCI COR. The Communication Plan shall also include a mechanism by which the NCI-OTS CDR and BCR coordinate on the frequency of data transmittal.

The contractor shall make available all the relevant information regarding the data models and vocabularies used for CPTAC information employed in their IT systems, API specifications, and other technical information needed by the NCI-OTS CDR. Any

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issues arising from licensing shall be brought to the attention of the NCI COR immediately when they are identified. The NCI-OTS CDR shall assume responsibility for ensuring that the UUID are properly assigned and transmitted.

The Contractor shall develop and execute a Data Use Agreement with the CPTAC DCC. NCI shall provide a cover memo describing NCI policies for CPTAC and a template DUA currently used within the project. The DUA addresses data ownerships issues, IP, patient privacy and confidentiality issues, and requires that researchers receiving data from the BCR shall not attempt to identify or re-contact donors, or their relatives. The Contractor shall provide TSS and BCR human subjects' documentation to the DCC as requested to support the DCC PI submissions to local IRBs.

E.8.b. Distributing the CPTAC Data to the DCC

Once the NCI-OTS CDR has established with the BCR that all local approvals are in place for receiving data and all agreements involving the BCR and the NCI-OTS CDR have been executed, the Contractor shall provide the requested data to the NCI-OTS CDR.

The Contractor will coordinate with the CPTAC NCI-OTS CDR to utilize the procedures developed in E.8.a to electronically transmit the covered clinical and sample date to the NCI-OTS CDR. It is expected that the transmissions will occur on a routine basis with the timing to be determined in consultation with the NCI-OTS CDR, the NCI COR, and the CPTAC Program staff.

E.9. Developing and Implementing Quality Control and Assurance Regimens for the Preparation of DNA and RNA

The Contractor shall develop and implement a control regimen to document the consistent quality of analytes it creates. QC data shall be captured in the Contractor's informatics systems and made available to the CPTAC NCI-OTS CDR. The QC data shall also be made available to the NCI COR, QMS, and others as approved by the NCI COR in a format to be determined during the Period of Performance.

The Contractor shall document and report biospecimen molecular extract quality data (specified below) for each type of analyte created, and these data shall be available online. The Contractor shall implement testing systems, including laboratory protocols and information systems to perform the following QC processes.

DNA and RNA shall be quantified using reproducible, high quality assays (e.g., a picogreen-based assay for DNA and an Agilent Bioanalyer-based assay for RNA); DNA quality shall be

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confirmed using a high-quality system (e.g., electrophoresis). QC criteria shall be established in collaboration with the CPTAC GCC when it is established and approved by the NCI COR and NCI CPTAC Program Staff. Only the DNAs and RNAs that meet the criteria shall be concentration normalized and stored. Only cases for which the RNAs meet the quality control criteria shall have any analytes (DNA and RNA) shipped to the GCC for characterization unless otherwise instructed by the NCI COR. All QC procedures shall be captured in SOPs.

The Contractor shall develop a protocol to distinguish between key reasons for molecular analyte production failure. Specifically, it shall establish a protocol to determine if the analyte failure is a function of the tissue specimen prior to processing or a function of the analyte isolation protocol performed by the Contractor. The protocol shall include the incorporation of known high quality "control" tissues and analytes into each tissue processing batch and molecular processing batch, respectively. Approval and implementation of this protocol shall be at the direction of the NCI COR.

The Contractor shall develop protocols to minimize or eliminate cross-contamination, and to measure rates of contamination.

The results of all QC processes, and the status of samples as they progress through QC, shall be electronically recorded in the LIMS and made available to NCI according to standard reporting mechanisms established.

E.10. General BCR Operations

E.10.a. Document Management

This SOW contains multiple references to documentation that the Contractor shall either receive from outside sources or develop internally. The Contractor shall use the electronic system provided for the Contractor hosted and managed by a third party for the storage of all electronic documents. In addition to the BCR staff and NCI COR, this system shall be accessible to the QMS personnel, NCI-OTS CDR personnel, and possibly others as determined by the NCI COR. The Contractor shall work with the hosting entity and the NCI COR to ensure that access to stored documentation is properly restricted based on the sensitivity of the documents.

Documents prepared internally by the BCR shall be versioned when appropriate. As a general rule, all older versions of documents shall be archived. Draft versions of documentation need not be archived unless, on a case-by-case basis, the Contractor is directed otherwise by the NCI COR.

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For documents dealing with content requiring NCI COR approval such as SOPs, the Contractor shall ensure that the relevant overseeing authority has approved the document and the document is so annotated.

E.10.b. Preparing Data Summaries/Dashboards on a Routine Basis

The Contractor shall prepare a summary document/dashboard of the inventory and status of all CPTAC specimens that are received or expects to receive based on the receipt of a "Submission" form from a TSS on a weekly basis. The summary shall be in the form of an electronic document prepared in a readily readable format (e.g., a Microsoft Excel spreadsheet). Further details regarding the content of the weekly report is detailed in the Acceptance Criteria below.

E.10.c. Preparing Standard Operating Procedures

This SOW contains multiple references to repetitive tasks requiring SOPs. At the initiation of the work, the Contractor shall identify all activities reasonably requiring the creation of a SOP and create an inventory of SOPs that will need to be created. Further details regarding the content of the inventory is detailed in the Acceptance Criteria below. Upon prioritization of the inventory by the NCI COR, the Contractor shall then develop those SOPs. All SOPs shall be reviewed and approved by the NCI CPTAC Program Staff and NCI COR.

It is envisioned that all SOPs will be made readily available to the participants in the CPTAC Program. The Contractor shall ensure that the SOPs accurately reflect the work performed and are of high quality. As the case with all CPTAC documentation, the SOPs shall be versioned.

E.10.d. Preparing Monthly Status Reports

The contractor shall create monthly status reports covering all aspects of the operation of the BCR including financials. Further details regarding the content of the Monthly Status Reports is detailed in the Acceptance Criteria below.

E.10.e. Project Close-Out Plan

The CPTAC Program views the tissues and data that will be collected under this SOW as a resource that will likely be used by CPTAC participants past the Period of Performance of this subcontract. The Contractor shall develop a Close-Out Plan describing their best judgment on the steps that would need to be taken by NCI to relocate the CPTAC data and information obtained under this SOW and any remaining tissue samples to a third-party. The intent is that the ongoing operations of the CPTAC BCR and the CPTAC-specific infrastructure that is developed will be

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consistent with the Close Out Plan enabling an efficient transfer of data and materials to a third party. The Contractor, working together with the NCI COR and the CPTAC Program Office, shall make all reasonable efforts to ensure that the BCR be operated with this Close-Out Plan in mind with the aim of simplifying and minimizing the costs to the NCI of a transition to a third party.

E.10.f. Communication Plans

This SOW contains several instances where a Communication Plan is required between or amongst the BCR and other stakeholders or CPTAC entities. The Contractor shall ensure that these Plans are created and executed on. Further details regarding the content of the Communications Plans are detailed in the Acceptance Criteria below.

F. Conformance and Compliance

F.1. Conformance to Section 508 Policies

All documentation and presentations prepared by the Contractor shall be Section 508 Compliant. Links to criteria and standards and general Section 508 information for The Department of Health and Human Services are found at: http://www.hhs.gov/web/508/. Information for documentation and presentations are found at http://www.hhs.gov/web/508/testdocuments.html.

F.2. Biosafety Considerations

Because this work shall involve the collection, storage, retrieval, laboratory processing, and transfer of human biological materials, the identification of biohazards and the minimization of exposure risk are important considerations for the design plan and implementation BCR.

Specific requirement(s) for biosafety include:

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F.2.a. All personnel involved in the handling, packaging and shipping of human biospecimens shall be trained in biosafety SOPs and adhere to all relevant regulations such as 29CFR Part 1910.1030, promulgated by the Occupational Safety and Health Administration (OSHA). Additional information on best practices for the collection, storage, and retrieval of human biological materials used in research is available from the International Society for Biological and Environmental Repositories (ISBER) at http://www.isber.org.

F.2.b. The Contractor shall implement a detailed plan for biorepository safety, including personnel training and monitoring.

F.2.c. The Contractor shall implement a detailed plan for laboratory safety, specifically including protocols for the handling of potentially infectious human biological materials.

F.2.d. Materials from non-human subjects shall be stored separate from human materials, if protocols from any source site or BCR Contractor require this separation.

F.3. IT Security Requirements

The Department of Health and Human Services (HHS) has a requirement that all IT systems meet the Federal Information Security Information Act (FISMA) compliance. The development and maintenance of these systems requires either a FISMA Certification and Accreditation (C&A) or a waiver.

F.4. Biorepository Certifications and Requirements

The Contractor shall handle genomic and clinical data that may be clinically relevant to the individuals from whom that sample was obtained. Current ethical practice and policy development in this area is not yet completely formalized; however, it is likely that some IRB approved protocols for this project shall require that clinically relevant findings generated during biorepository operations shall be passed back to the clinical setting (see patient re-contact section). Therefore, the Contractor shall minimally require CLIA certification for the pathology component.

The Contractor shall be working with patient data either transmitted with biospecimens acquired from legacy repositories or from prospective collections. In either case, the overall program supported by BCR/Contractor shall be subject to the "Common Rule" (45CFR46) for the protection of human subjects. The BCR shall obtain a Certificate of Confidentiality (http://grants1.nih.gov/grants/policy/coc/appl_extramural.htm) to cover itself and the TSS providing samples and data to it.

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All security and access policies for each system will be followed (reference A005 International Society for Biological and Environmental Repositories - 2008 Best Practices for Repositories Collection, Storage, Retrieval and Distribution of Biological Materials for Research in Appendix D).

G. Deliverables

The following table contains a list of deliverables with due dates. All days identified are intended to be normal business days unless otherwise specified. The Contractor may suggest an alternative due date for any or all deliverables in their offer. The final schedule will be agreed to by the NCI COR and the Contractor based on the Contractor's proposed cost and proposed delivery schedule.

Deliverable	Due Date
Project Plan for Initiating Operations	Initial version with proposal; final version five days after the kick off meeting.
BCR Operation Management Plan	Initial version with proposal; final version 30 days after subcontract execution
BCR Monthly Status Report	10th of each month
BCR Monthly Financial :Status Report	10th of each month
BCR Weekly Dashboard	Each Friday
IT Security Assessment and Security Plan	Initial version with proposal; final version 30 days after subcontract execution
IT Architecture and Design	Initial version with proposal; final version 30 days after subcontract execution
IT Maintenance and Backup Documentation	Initial version with proposal; final version 30 days after subcontract execution
SOP Inventory and Development Plan	Initial version with proposal; final version 30 days after subcontract execution

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Deliverable	Due Date
Standard Operating Procedures	Per SOP Inventory and Development Plan
TSS Communication Plan	Initial version with proposal; final version 15 days after subcontract execution
DCC Communication Plan	Initial version 30 days after contract execution; final version 30 days after acceptance of the initial version.
PCC Communication Plan	Initial version 30 days after contract execution; final version 30 days after acceptance of the initial version.
GCC Communication Plan	Initial version 30 days after contract execution; final version 30 days after acceptance of the initial version.
Certifications	When obtained
Project Close Out Plan	Initial version 60 days after subcontract initiation; final version 30 days after acceptance.
Project Summary Report	Initial version 60 days before the end of the Period of Performance; final version 1 day before the end of the Period of Performance.

G.1. Deliverable Description and Acceptance Criteria

G.1.a. Project Plan for Initiating Operations

The Project Plan for initiating operations shall detail the Contractor's approach and timelines for becoming fully functional. The plan shall describe the

1. Timelines
2. Scale up staffing
3. Resources required
4. Dependencies

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The Plan shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF; attachments in Microsoft Project).

Acceptance Criteria

The Project Plan will be considered acceptable if it is submitted in the format required and describes an approach for rapidly and economically bringing the BCR on line. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.b. BCR Operation Management Plan

The BCR Operations Management Plan shall detail the Contractor's approach to managing the BCR. The BCR Operation Plan shall describe the structure and day-to-day operations of the BCR as well as a Project Plan describing the steps needed to begin operations. The BCR Operation Plan shall consist of the following elements:

1. Work Breakdown Structure
2. Major Workflows as Cross-Functional Flowcharts
3. Resource Management Plan
4. Organizational chart covering major BCR functions including:
    a. Roles and Responsibilities covering specific BCR functions (clinical outreach, pathology review, molecular isolation, quality program at a minimum)
    b. Allocation of staff
5. Service level and response times and mechanisms for responding to stakeholder/participant inquiries
6. Internal Communication Plan including interactions with the NCI COR.
7. Training of BCR personnel
8. Training of TSS personnel
9. Control of Government Furnished Information/Equipment
10. Certifications and approvals
11. Safety Plan
    a. Biorepository
    b. Laboratory

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12. Risk Matrix and Management including:
    a. Identifiable risks and severity
    b. Mitigation strategies

The Plan shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF; attachments in Microsoft Project).

Acceptance Criteria

The Operations Plan will be considered acceptable if it is submitted in the format required and describes an operational approach that satisfies the requirements of the SOW. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.c. BCR Monthly Status Report

The Monthly Operations Status Report shall provide a comprehensive view of the status of the BCR and include:

1. The most recent BCR Dashboard.
2. Specific listings of tissue samples and analyte samples that have failed QC, and the reason for failure.
3. Administrative status of all CPTAC entities towards being able to ship samples and data to or from the BCR.
4. Data uploads to the DCC.
5. Listing of new/revised SOPs including hyperlinks to the SOPs in the document storage system.
6. Listing of new/revised CRFs.
7. Outwardly facing communications including but not limited to presentations by staff and training of TSSs.
8. Identified issues and risks along with remediation strategies.
9. Informatics Systems Report (LIMS, Biorepository, informatics.)
    a. Changes to the Data Models
    b. Usage estimates
    c. Confirmation of backup

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d. Required or proposed system updates/modifications for interactions with the CPTAC NCI-OTS CDR. Including timelines for implementation.

Note that many of the items covered in the Monthly Status Report will likely also be covered in the weekly dashboard report. Where possible, the most recent dashboard may be included to cover these items.

The Report shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF; attachments in Microsoft Excel).

Acceptance Criteria

The Monthly Status Report will be considered acceptable if it is submitted in the format required and fully describes all of the required elements. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.d. BCR Monthly Financial Status Report

The Monthly Technical Status Report shall provide a comprehensive view of the financial status of the BCR and include:

1. Hours worked by resource
2. Current period expenditures and contract year to date
3. Estimate At Completion (EAC)
4. Changes to the expected monthly burn rate for the duration of the effort

The Monthly Financial Status Report shall be sent in Adobe PDF or Microsoft Word or Excel format directly to the NCI COR

Acceptance Criteria

Acceptable Financial Status Reports shall include the above information, in the formats requested, in sufficient detail to provide a comprehensive picture of the current financial status of the BCR. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

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G.1.e. BCR Weekly Dashboard

The Weekly Dashboard shall provide a comprehensive view of the inventory status of the BCR. This document will be made available to all CPTAC participants. The Dashboard shall include:

1. Cases, samples and clinical data received categorized by source site, cancer, tumor vs. normal, processing batch, and number of samples per case.
2. Current tissue inventory categorized by source site, diagnosis, format, and including pathology verification status/result and clinical data elements.
3. Current analyte inventory categorized by analyte, and including aliquot status, initial amount, remaining amount, and amount distributed.
4. Samples processed categorized by analyte produced, including QC results.
5. DNA and RNA aliquots distributed categorized by analyte type, diagnosis, source tissue sample, and source analyte sample.
6. Biospecimens distributed to the PCCs categorized by recipient site and biospecimen type.
7. Current status and results for samples in pathology and molecular analyte production processes. For each tumor type, include:
    a. Cases received
    b. cases pending pathology review
    c. cases which passed pathology review
    d. cases which failed pathology review
    e. cases pending molecular review
    f. cases which passed molecular review
    g. cases which failed molecular review
8. Current status of clinical data collection categorized by TSS, case, cancer, including data completion rates at the level of TSS, case, form, and data element.
9. Projected sample receipts by tumor type based on TSS “Submission” forms received.

The Report shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF; attachments in Microsoft Excel).

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Acceptance Criteria

The Monthly Status Report will be considered acceptable if it is submitted in the format required and fully describes all of the required elements. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.f. IT Security Assessment and Security Plan

The IT Security Assessment and Security Plan shall be patterned after NIST Special Publication 800-30, Revision 1 and NIST Special Publication 800-18, Rev 1 respectively. The Contractor shall assume that the Integrity, Confidentiality, and Availability of the systems operated for this SOW containing CPTAC information and CPTAC information would each be categorized as "Moderate" as defined in the NIST FIPS PUB 199.

The Report shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF; attachments in Microsoft Excel, Visio, or similar).

Acceptance Criteria

The Plans will be considered acceptable if they are submitted in the format required and fully describe all of the required elements. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.g. IT Architecture and Design

The IT Architecture and Design shall describe in diagrams and narrative the overall IT system including the major hardware and software components along with established connections between the components.

The Report shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF; attachments in Microsoft Visio, or similar).

Acceptance Criteria

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G.1.h. The Plans will be considered acceptable if they are submitted in the format required and could be used to by a third party well-versed in IT systems to receive and utilize CPTAC data downloads from the BCR. The deliverable shall adhere to the general acceptance criteria and as far as practical shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html

G.1.i. IT Maintenance and Backup Documentation

The report shall describe the routine processes and procedure employed by the Contractor to maintain the systems used for CPTAC data as well as the backing up of CPTAC data.

The Report shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF; attachments in Microsoft Visio, or similar).

Acceptance Criteria

The documentation will be considered acceptable if they submitted in the format required and could be used to by a third party well-versed in IT systems to receive and utilize CPTAC data downloads from the BCR. The deliverable shall adhere to the general acceptance criteria and as far as practical shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html

G.1.j. SOP Inventory and Development Plan

The SOP Inventory and Development Plan should list all the SOPs reasonably expected to be required for the execution of the repetitive tasks contained in this SOW. The Plan should include:

1. A prioritized listing of all SOPs that may be needed.
2. Timelines for developing the SOPs including approval by the NCI CPTAC Program Office and NCI COR.

The Plan shall be submitted to the NCI COR in a suitable electronic format (e.g., Microsoft Excel format).

Acceptance Criteria

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An acceptable SOP Inventory and Development Plan shall include the above information, in the formats requested, and provide a comprehensive list of the SOPs required and the timelines for developing the SOPs. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.k. Standard Operating Procedures

Standard Operating Procedures shall be developed and approved based on the final SOP Inventory and Development Plan. All SOPs shall fully describe the procedure and adhere to a similar format to be determined by the BCR. SOPs shall be versioned and updated as needed.

SOPs shall be created and submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF format). Submission may be in the form of hyperlinks to SOPs in the document storage system.

Acceptance Criteria

Acceptable SOPs shall include all relevant information regarding the procedure covered and contain sufficient detail so that a specialist or scientist is capable of reproducing all aspects of the procedure. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.l. TSS Communication Plan

The TSS Communication Plan shall identify the methods by which the BCR will communicate with the CPTAC TSSs. The Plan shall include:

1. Training of TSS staff
2. Scheduling of routine communication
3. Scheduling of shipping
4. Method for resolving defects in clinical, biospecimen, and pathology data/information submitted by the TSS
5. Method for resolving biospecimen quality issues that might arise.

The Plan shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF format).

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Acceptance Criteria

The Plan will be considered acceptable if it is submitted in the format required and fully describes all of the required elements. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.m. NCI-OTS CDR Communication Plan

The NCI-OTS CDR Communication Plan shall identify the methods by which the BCR will communicate with the CPTAC NCI-OTS CDR. The Plan shall include:

1. Scheduling of routine communication.
2. Method for supplying the data model to be employed, IT system information, and other input needed by the NCI-OTS CDR for determining appropriate data formats and data transmission protocols.
3. Method for interacting with the CPTAC NCI-OTS CDR in developing any project plans involving both the BCR and NCI-OTS CDR for implementing changes to the systems employed at either entity.
4. Scheduling of data uploads.
5. Method for resolving data quality issues that might arise.

The Plan shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF format).

Acceptance Criteria

The Plan will be considered acceptable if it is submitted in the format required and fully describes all of the required elements. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.n. PCC Communication Plan

The PCC Communication Plan shall identify the methods by which the BCR will communicate with the CPTAC PCC. The Plan shall include:

1. Scheduling of routine communication.

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2. Method for receiving requests from the PCCs for biospecimens and shipping biospecimens.
3. Method for resolving shipping or biospecimen quality issues that might arise.

The Plan shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF format).

Acceptance Criteria

The Plan will be considered acceptable if it is submitted in the format required and fully describes all of the required elements. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

G.1.o. GCC Communication Plan

The GCC Communication Plan shall identify the methods by which the BCR will communicate with the CPTAC GCC. The Plan shall include:

1. Scheduling of routine communication.
2. Method for supplying the data model to be employed, IT system information, and other input needed by the GCC for determining appropriate data formats and data transmission protocols.
3. Method for interacting with the CPTAC GCC in developing any project plans involving both the BCR and GCC for implementing changes to the systems employed at either entity.
4. Scheduling of data uploads.
5. Method for resolving data quality issues that might arise.

The Plan shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF format).

Acceptance Criteria

The Plan will be considered acceptable if it is submitted in the format required and fully describes all of the required elements. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

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G.1.p. Annual Certifications and Approvals

The following certifications shall be confirmed in writing with the frequencies noted in the relevant Sections of the SOW. The content should conform to that noted in the relevant sections of the SOW. The format is at the discretion of the Contractor.

1. Approval from Contractor's IRB
2. Certificates of Confidentiality
3. Human subjects documentation directly relating to the BCR
4. Material Transfer Agreements between the BCR and other CPTAC entities
5. Section 508 Compliance report
6. Safety Plan
7. TSS Training

Acceptance Criteria

The documentation will be considered acceptable if approvals have been granted and all the elements generally required for each item have been addressed.

G.1.q. Project Close-Out Plan

The Close-Out Plan shall describe the Contractor's best judgment regarding the processes for transferring all materials and data to the government or a new vendor. The initial version of the Plan shall be submitted for review and modification six months after the initiation of the project. The final version shall be delivered three months later.

The Plan shall be submitted in a suitable electronic format (e.g., Microsoft Word or Adobe PDF format).

Acceptance Criteria

The Plan will be considered acceptable if it is submitted in the format required and describes the required elements in sufficient detail for a third-party, well-versed in biobanking and IT systems management, to receive the data and materials in and resume operations of the BCR in collaboration with the BCR, NCI COR, and CTPAC Program Office staff.

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G.1.r. Project Summary

The Project Summary Report shall describe the work accomplished against each task in this Statement of Work and its success in meeting the goals and objectives of the project. All major accomplishments produced by this work shall be described. Any issues encountered, resolutions, and lessons learned shall also be given.

In addition, the following shall be provided:

1. An inventory of:
   a. Residual tissues and analytes.
   b. Histopathology images and slides.
   c. SOPs.
2. Government Furnished Equipment
3. A complete download of the content of the LIMS system, Biorepository, and any other informatics systems used

The Project Summary Report shall be sent directly to the NCI COR. The narrative components shall be in Adobe PDF or Microsoft Word format. The inventories shall be in Microsoft Excel format or as defined by the NCI COR. Download of the informatics system, biorepository, and any other informatics systems used shall be in an electronic format to be determined.

Acceptance Criteria

Acceptable Project Summary Reports will include all of the above information, in sufficient detail so that a reader familiar with this SOW will be able to judge progress against all tasks in the SOW. The deliverable shall adhere to the general acceptance criteria and shall follow Section 508 compliance guidance (§ 1194.1, § 1194.2, and § 1194.41 subpart D. Information on Section 508 compliance can be found at http://www.hhs.gov/web/508/accessiblefiles/index.html.

The criteria for an acceptable data download are to be determined.

G.2. General Acceptance Criteria

In addition to specific acceptance criteria listed above, general quality measures, as set forth below, will be applied to each deliverable received from the Contractor under this Statement of Work.

Accuracy – Deliverables shall be accurate in presentation, technical content, and adherence to accepted elements of style.

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Clarity – Deliverables shall be clear and concise. Any/all diagrams shall be easy to understand and be relevant to the supporting narrative.

Consistency to Requirements – All deliverables must satisfy the requirements of this Statement of Work.

Timeliness – Deliverables shall be submitted on or before the due date specified in this Statement of Work or the PMP, or submitted in accordance with a later scheduled date determined by the Government.

G.3. Deliverable Process

G.3.a. Format and Delivery

Monthly Reports and any documents containing sensitive information such as financials shall be sent via email directly to the NCI COR. These reports shall be sent in the format as specified by the NCI COR.

G.3.b. Review and Acceptance

For all deliverables, the NCI COR will perform an evaluation for each deliverable using acceptance criteria provided above. Approval/rejection notice will be sent to the Contractor within 30 calendar days of receipt of the deliverable. If deliverables meet the acceptance criteria, the NCI Contracting Officer will issue the Contractor a written acceptance through email that acknowledges both receipt and overall acceptance of the deliverable. Irrespective of payment status for subject deliverable, Contractor should not assume acceptance has been made without formal notification from the NCI CO. If deliverables do not meet the acceptance criteria, all issues will be described unambiguously and sent to the Contractor via email. The Contractor will then address each issue or state why the issue may not be addressed and resubmit the deliverable. Resubmitted deliverables will be reviewed within 15 calendar days.

Absence of any comments by the NCI CO will not relieve the Contractor of the responsibility for complying with requirements in this Statement of Work. Final approval and acceptance of documentation required herein shall be by letter of approval by the NCI CO. The Contractor shall not construe any letter of acknowledgment of receipt material as a waiver of review or as an acknowledgment that the material is in conformance with this.

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H. Meetings

H.1. Kick Off

An initial kick off meeting will be held within 7 calendar days of award or as agreed to by the NCI COR. This will be attended by the NCI COR, and others deemed relevant by the NCI COR. Key Contractor personnel as well as a representative from the Contractor's contracts organization are required to attend. The intent of the kickoff is for all key personnel to meet to discuss the project's overall technical and contractual requirements.

At this meeting, the Contractor shall be prepared to discuss the following:

A. Technical objectives
B. Preliminary Operations Plan
C. Deliverables and deliverable acceptance criteria

H.2. Monthly Project Meeting

A monthly teleconference will be held with the NCI COR, NCI CPTAC Program Staff, and BCR Leadership to review performance of the BCR, the last Monthly Status Report, and the last Dashboard.

H.3. Monthly TSS Meeting

A monthly teleconference will be held amongst the BCR, all the TSSs, the NCI COR(s), and the NCI CPTAC Program staff to discuss progress of the tissue procurement and issues that may have arisen. The BCR shall attend this meeting.

I. Place of Performance

The work will be performed at the vendor's facilities.

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J. Period of Performance

The base Period of Performance will be one year with up to four option periods of one year each.

K. Government Furnished Data, Material, or Equipment

None

L. Additional Intellectual Property Considerations

CPTAC complies with all current NIH requirements regarding IP as well as FAR 52.227.11 and FAR 52.227.14

A major goal of the CPTAC is to maximize the benefits of all work funded as part of the CPTAC Program for the improvement of public health through discoveries of the scientific community. CPTAC data sharing and data release policies provide for a broad freedom-to-operate for all users of CPTAC data by rapidly placing all data in the public domain. The CPTAC policy is to ensure that this data is unencumbered by intellectual property claims. In addition to data, any algorithm produced specifically to analyze CPTAC data, software source code or other resource made possible under the auspices of CPTAC will be made available to the public domain without intellectual property restrictions.

It is expected that any data producer for CPTAC (whether supported by a grant or contract mechanism) will make all information available, without requirement for licensing, for applications such as, but not necessarily limited to, the use of markers in developing assays or targets for therapeutics and diagnostics. CPTAC encourages broad use of this data coupled with a responsible approach to management of intellectual property derived from downstream discoveries that are consistent both with the recommendations cited in NIH's Best Practices for the Licensing of Genomic Inventions and the NIH Research Tools Policy.

The filing of patent applications in a manner that would restrict use of CPTAC data, software and other resources could substantially diminish the value and public benefit provided by this program. The Contractor acknowledges the CPTAC goal to sustain the public benefit of CPTAC and will not pursue intellectual property protections that would prevent or block access to, or use of, any element of data, conclusions drawn directly from those data, software or other resources made available through the CPTAC program.

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APPENDIX 1 – ACRONYMS

List of Acronyms

BCR – Biospecimen Core Resource
CDR – Comprehensive Data Resource
CO – Contracting Officer
COR – Contracting Officer's Representative
CPTAC – Clinical Proteomics Tumor Analysis Consortium
DCC – Data Coordinating Center
DNA – Deoxyribonucleic Acid
DUA – Data Use Agreement
Genome Characterization Center
HIPAA – Health Insurance Portability and Accountability Act
IRB – Institutional Review Board
LDS – Limited data set
MTA – Material Transfer Agreements
NCI – National Cancer Institute
PCC – Proteome Characterization Center
PHI – Protected Health Information
PMP – Project Management Plan
QC – Quality Control
RNA – Ribonucleic Acid
SOP – Standard Operating Procedures
SOW – Statement of Work
SA – Subcontract Administrator
TCGA – The Cancer Genome Atlas
TPM – Technical Project Manager
TSS – Tissue Source Site

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APPENDIX 2

ACCEPTABLE TUMOR TYPES AND COLLECTION PROTOCOLS

Tumor Types
Lung Adenocarcinoma
Pancreatic Ductal Adenocarcinoma
Glioblastoma Multiforme
Acute Myeloid Leukemia
Clear Cell Renal Cell Carcinoma
Head and Neck Squamous Cell Carcinoma
Cutaneous Melanoma
Sarcoma
Lung Squamous Cell Carcinoma
Uterine Corpus Endometrial Carcinoma

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APPENDIX 3 – IRB GUIDANCE DOCUMENT

The purpose of this document is to assist Institutional Review Boards (IRBs)/Ethics Boards and/or Privacy Boards at participating clinical sites in their review of protocols that include submission of tissues and associated clinical data to The Clinical Proteomics Tumor Analysis Consortium (CPTAC) Project of the National Cancer Institute (NCI) of the National Institutes of Health (NIH). This document provides summary information on the project and how it works, followed by a discussion of key points of interest to this audience.

A. CPTAC Aim and Summary

The overarching goal of CPTAC is to improve our ability to diagnose, treat, and prevent cancer. To achieve this goal in a scientifically rigorous manner, the National Cancer Institute (NCI) launched CPTAC to systematically identify proteins that derive from alterations in cancer genomes and related biological processes, and provide this data with accompanying assays and protocols to the public.

Genomics initiatives such as The Cancer Genome Atlas (TCGA) have characterized and sequenced the genomic alterations from several types of cancer. These efforts are providing a catalogue of alterations in the cancer genomes and setting the stage for the development of more molecular interventions. CPTAC will leverage its analytical outputs from previous phases in the coming years by producing a unique continuum that defines the proteins translated from cancer genomes in order to link genotype to proteotype and ultimately to phenotype. This goal will be met through four overarching objectives. They are:

Objective 1: Identify and characterize the protein inventory from tumor and normal tissue biospecimens

Objective 2: Integrate genomic and proteomic data from analysis of common cancer biospecimens

Objective 3: Develop assays against proteins prioritized in the discovery stage as potential biomarker candidates

Objective 4: Perform testing of verification assays in relevant cohorts of biospecimens

For the cancer types studied, approximately 200 cases of tumor tissue with a case-matched germline DNA source that have will be genomically analyzed across multiple genomic platforms will be characterized by large-scale, quantitative protein profiling via mass spectrometry. When possible, matched normal tissue for each case will be included in the analyses. Each case will be obtained with demographic and clinical annotation, along with follow-up information minimally sufficient to correlate molecular profiles with survival.

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CPTAC is operating as a network of grant and contract funded entities. With regard to prospective human sample collection, clinically annotated tissue specimens will be collected from several participating CPTAC Tissue Source Sites (TSS), and sent to the CPTAC Biospecimen Core Resource (BCR). The BCR will perform quality control on the tissues and will send qualified samples to the CPTAC Protein Characterization Centers (PCC) for proteomic analysis. The BCR will use uniform protocols to isolate nucleic acids that will be sent to a Genome Characterization Center (GCC) within the network for genomic analysis. The PCC and GCC data are sent to the CPTAC Data Coordination Center (DCC), where the data are made available to other investigators via the internet. Raw sequencing data may be maintained by a separate DCC than the rest of the CPTAC data. The BCR, along with the NCI-OTS CDR and QMS, will also standardize and quality control the participant clinical data that are subsequently sent to the central NCI-OTS CDR.

The GCC molecular characterizations will include whole-exome sequencing, micro- and messenger-RNA expression profiling (sequenced based), and chromosomal structure and copy number alteration (low pass sequence and/or chip based). Since both tumor and germline DNA are sequenced from each case, somatic single nucleotide variants are discovered. However, the germline information is also available for which investigators can use for their research. Proteomic characterization of these samples by the PCCs will include mass spectrometry-based profiling of the proteome, phosphoproteome, and glycoproteome of both the tumor and nonmalignant specimens for each qualified case. A subset of selected samples may also be characterized by protein microarray and/or reverse-phase protein array.

B. Key Human Subjects Policies

This document was written to provide guidance to Principal Investigators and IRB staffs at the CPTAC TSSs at which the participants are enrolled and their tissue specimens and clinical data are collected. CPTAC will collect tissues and associated clinical data from US-based organizations.

U.S.-based sites are subject to federal regulations covering human subjects research (45 CFR 46, the "Common Rule") and are also HIPAA "Covered Entities." The following sections describe key CPTAC protocols and policies relevant to human subject research and participant protection policies.

C. Minimal Risk Protocol

To date, most IRBs have considered protocols providing clinically annotated tumor tissues to programs such as The Cancer Genome Atlas (TCGA) program sponsored by the National Cancer Institute (NCI) and National Human Genome Research Institutes (NHGRI) to be "minimal risk." The CTPAC program will mimic TCGA program in all aspects relating to patient risk. The CPTAC program will employ a series of prospective protocols for tissue acquisition that are non-interventional and will employ a "surgical remnant" or "surgical discard" approach; i.e., the tissues to be collected will be obtained during the normal course of care for cancer patients that would normally be discarded or used in other research programs. Participants are at some "social risk" from potential loss of privacy or the possibility of a

security breach resulting in a loss of confidentiality of their medical information. Participation in CPTAC holds an additional social risk: the project generates individually unique proteomic and genetic information (see Section G [Genetic Data: Open vs. Controlled-Access Tiers] below) and there is a theoretical risk that such data combined with third-party databases could result in re-identification of a participant.

With "minimal risk" protocols, IRBs may wish to consider applications or amendments to existing protocols under an expedited review process.

D. Linked Protocol and "Coded" Identifiers

Similar to TCGA, CPTAC will operate as a "linked" protocol, with each participant ID being doubly de-referenced (i.e., "coded" twice) before tissue or data are distributed by the Network. The first linking key is retained by the TSS at which the participants are enrolled. Access to this key is the purview of TSS institutional policies and the local IRB. The second linking key is retained by the CPTAC BCR and is only made available within the program for quality control purposes upon approval by the Director, Office of Cancer Clinical Proteomics Research. The second key will also be provided to the TSS Principal Investigator upon presentation of IRB approval to have this second key. As a result of these policies, investigators using CPTAC data are prevented from seeing participant direct identifiers or from linking backwards to the primary participant identifiers at the TSS clinical sites by both technical systems and contractual obligations.

"45 CFR 46.101(b)(4)Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects"

E. HIPAA and Collection of a Limited Data Set (LDS)

Clinical data will be provided by the CPTAC TSS to the CPTAC BCR in a form compliant with a HIPAA-defined Limited Data Set (LDS) (The 16 traditional direct identifiers as defined by HIPAA under 45 CFR 164.514(e)(2), name, social security number, etc. are excluded). Additionally, CPTAC will not collect geographic information at the level of detail permitted by an LDS. CPTAC will collect specific demographic and clinical event date information, for example, country of origin, dates of birth, death, admission, diagnosis, surgery, treatment, and release. These data are necessary for quality control purposes and to enable correlation of molecular profiles with time-based patient characteristics such as survival. It is expected that the organization hosting the BCR will be a contractor to NCI and the BCR and NCI will enter into HIPAA-compliant Data Use Agreements (DUA) with the clinical Tissue Source Sites (the HIPAA "Covered Entity") to enable this process.

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However, LDS data will **not** be distributed beyond the CPTAC NCI-OTS CDR to any other CPTAC network component, (PCC and GCC) nor to the broader research community. Prior to data distribution, the NCI-OTS CDR will convert all dates to intervals and/or modify dates to being no more specific than one year. As a result, distributed participant data meet the HIPAA test of being De-Identified (45 CFR 164.514(b)(2)(i)).

F. Informed Consent

CPTAC policy is that subjects enrolled for tissue collections must be consented under a protocol that does not expressly conflict with any key concepts related to participation in CPTAC.

G. Genetic Data: Open vs. Controlled-Access Tiers

In addition to proteomic data, CPTAC will generate individually unique genetic data ("genetic fingerprints", or genotypes). These data will not be directly tied to an identified individual, and the clinical information associated with these data are de-identified as described above. Nevertheless, a theoretical risk exists that the genetic data in conjunction with third party databases (e.g., forensic genetic profile databases) could lead to the re-identification of a participant or relative. Consequently, NIH policy for CPTAC will be the same as for TCGA in that individual genetic data from the characterization studies will be kept in a restricted-access database. (More information on segmentation of all CPTAC data between the open-access and restricted-access tiers is in Section I2 below.)

To be authorized to access the restricted tier of data, Investigators will be required to submit an application to the project's Data Access Committee (DAC). Upon approval by the DAC that the access request is for bona fide research purposes, the Investigator and their institution will be required to subscribe to a Data Use Certification that controls their ability to access the data, and places requirements for data security upon them, scientists directly under their control, and their institutions. Data use for these controlled-access data are for any legitimate research use (i.e. there are no data use restrictions and users may apply data to non-cancer research-related discovery).

H. IRB documentation of approval to participate

NIH policy regarding TSS participation in CPTAC places 45CFR46 compliance responsibility on the local IRB. Nevertheless, to participate, each TSS Principal Investigator must have some level of IRB review and document such review to the NCI, and the BCR. Such review can range from a full IRB protocol submission and approval, amendment to an existing protocol, or an expedited/administrative review. The IRB may determine that participation is either Exempt or grant a Waiver, either of which is acceptable to NIH. Also, the IRB may determine that participation is not human subjects research, if, for example, the subjects are deceased.

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Regardless of the IRB finding, however, program policy is that a TSS Principal Investigator must document to NCI and the BCR that their IRBs have either:

1. approved their participation specifically in the CPTAC project, through an approved protocol, amendment, exemption, or waiver; or
2. provided documentation that the IRB does not consider participation to constitute "human subjects research," and therefore does not have purview.

I. Additional information on CPTAC Policies

I.1. Human Subjects and Participant Protection

CPTAC expects investigators, their institutions, and their IRBs to consider, based on their own standards of research practice, whether or not research involving coded and potentially re-identifiable information in CPTAC datasets meets the definition of "human subjects research" or not. The NCI presumes that this determination will be made consistent with institutional policies and under the auspices of the local IRB.

I.1.a. Contents of Informed Consent, additional information

For the purpose of reviewing the content of Informed Consents for prospective collections, the following key concepts pertinent to CPTAC should be considered for inclusion and disclosure to participants:

- genetic research, including proteomic analysis and DNA sequencing
- sharing of biospecimens, including to collaborators at other institutions
- sharing of clinical data, including to collaborators at other institutions
- possibility of future research use
- use of internet-connected electronic database with restricted public access
- the risk of loss of privacy or confidentiality of their personal information
- there will be no return of individual results to the participant
- should a patient withdraw, the project cannot retrieve or delete data once they have been distributed. Residual tissue at the BCR will no longer be used.

CPTAC may develop Informed Consent templates with suggested language that includes the concepts above, with specific nuances for prospective tissue procurement protocols.

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I.2. Data Sharing and Access

I.2.a. Rapid and Broad Data Release

CPTAC policy is to promote wide dissemination of all project data for use by the biomedical research community and to assure their maximum utility. Accordingly, CPTAC is committed to the rapid and complete release of its datasets for use by all investigators throughout the global scientific community who, along with their institutions, certify their agreement with CPTAC policies.

I.2.b. Data Access: open- versus restricted-access tiers

To minimize the risk of participant identification, the CPTAC Project Team established a policy that CPTAC data be made available from a two-tiered data access system.

- The Open-Access Data Tier will be publicly accessible to anyone on the internet and contain only proteomic, genomic, and clinical data that cannot be analyzed to generate a dataset unique to an individual. These data may include:
  - Tissue pathology data
  - HIPAA de-identified clinical data
  - Gene expression data
  - Copy-number alterations for non-genetic platforms
  - Proteomic data
  - Data summaries, such as genotype frequencies
  - DNA sequence data of single amplicons
- The Controlled-Access Data Tier will contain genomic and clinical data that are associated to a unique, but not directly identified, person. However, there is a risk that these data could be analyzed to potentially identify a person through reference to 3rd party databases. They will therefore be managed with both additional technical security and a qualification and access authorization process for investigators and their institutions. They will be made available to any qualified researcher for the purpose of biomedical research, once the investigator, along with his/her institution, has certified agreement to the statements within TCGA Data Use Certification (DUC). The DUC can be found at:

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- http://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=DUC&view_pdf&stacc=phs000178.v4.p4

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