

# **Networks of Tissue Source Sites (TSS) Supporting NCI's The Cancer Genome Atlas program**

## **1 Background and Introduction**

The National Cancer Institute is expanding its basic and translational research programs that rely heavily on sufficient availability of high quality well annotated biospecimens suitable for use in genomic studies. The NCI's overarching goal with such programs is to improve the ability to diagnose, treat, and prevent cancer.

The Cancer Genome Atlas (TCGA), one such program, is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies. The National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) launched TCGA as a 3-year pilot project in 2006, and have since (August 2009) initiated the second phase of the project to study at least 20 additional cancers over 5 years. This project aims to systematically explore the entire spectrum of genomic changes involved in human cancer. Specifically, the project is designed to comprehensively analyze DNA copy number changes, including large (on the order of chromosome segments) and small (1,000-100,000 kb) scale rearrangements, transcription profiles, epigenetic modifications, sequence variation, and sequence in both tumor tissue and case-matched germline DNA. The suite of analysis platforms will be applied to a common set of molecular analytes obtained from clinically annotated high-quality tumor biospecimens and case-matched normal tissue (control). More detailed information can be found at the project's website: <http://cancergenome.nih.gov>. To successfully generate comprehensive data, TCGA will need in excess of 40,000 biospecimens over course of the project.

The contractor shall provide clinically annotated biospecimens to TCGA.

## **2 Statement of Work**

Independently and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government as needed to perform the following:

The Contractor shall establish Tissue Source Site (TSS) networks capable of delivering clinically annotated biospecimens. The tissues and data shall be delivered to one of TCGA's Biospecimen Core Resource(s) (BCR) for storage, quality control, processing into molecular analytes, and other research efforts. Information regarding the name of the TCGA BCR will be provided to the Contractor after contract award. The histological specifications and annotation

requirements of the cancers to be studied by TCGA, the number of cases and biospecimens required per cancer, and preferred timing for their delivery to a BCR will be determined at a later date.

The Contractor shall be responsible for administratively and financially establishing, managing, coordinating and operating relationships with multiple TSS.

- The Contractor does NOT necessarily need their own biorepository capabilities. Under this contract, biospecimens and data shall be shipped directly from the TSS to a TCGA BCR, without transshipment through an intermediate site.
- A tissue Accrual Plan that details the accrual capabilities of each TSS and the distribution and timing of collection for specific cancer types, and which describes the quality management program used to monitor and control tissue accrual shall be required.
- The logistics and protocols governing transfer of biospecimens and data from TSS to BCR will be directed by the BCR assigned to receive materials from that particular TSS.
- This contract is agnostic about whether clinically annotated cancer biospecimens are obtained from retrospective collections and/or from prospective protocols, provided that the biospecimens and data meet TCGA specifications. It is anticipated that the majority of biospecimens will be prospectively obtained. However, if a TSS already has retrospective material collected under the same or similar protocols as would be used prospectively for this work, such biospecimens and data may be delivered under this SOW. When both options are available, retrospective biospecimens are preferred so that samples are more quickly obtainable and outcomes data are more immediately available.
- This SOW anticipates that Offerors will primarily represent networks of TSS; however, that is not a requirement. Individual TSS may respond, and will be reviewed upon the bases described herein, especially their ability to provide sufficient numbers of materials over the course of the contract.
- Entities capable of enrolling participants and providing materials from cancers of less frequent incidence are especially encouraged to respond.

This SOW is divided into three requirements sections below. The first section states the requirements for biospecimens, data and policy adherence for the TSS providing them; the Contractor shall pass these requirements through to its TSS network members. The second section specifies the Contractor's requirements for enrolling and monitoring its TSS Network members. The third section states requirements applicable directly to the Contractor.

## ***2.1 Requirements for Policies, Biospecimens and Data***

NCI and NIH have established a number of policy and technical requirements that must be adhered to by TSS contributing biospecimens to TCGA. For work performed under this contract, the Contractor shall establish these requirements with all of its TSS network members. Upon contract award, the Contractor shall submit a comprehensive portfolio of the

existing network membership, with evidence that all of the following policy, biospecimen, and data requirements have been established within its network agreements. The TSS network members are not expected to remain static, and Contractor shall update the portfolio with changes that occur over the term of the contract. The network portfolio shall also address its policies and procedures for risk mitigation and recourse available to the Contractor and NCI should a network member fail to meet its obligations.

### **2.1.1 TCGA policy requirements**

The following administrative and policy requirements must be inherent in all relationships resulting in delivery of annotated biospecimen procurement for TCGA.

#### **2.1.1.1 NCI site visit of tissue source sites**

The Contractor shall provide to the NCI Contracting Officer's Technical Representative (COTR) the names of all sites and administrative contacts in their TSS networks, and names of principle investigators on IRB-approved protocols obtaining biospecimens at those sites for delivery to TCGA. NCI reserves the right to perform site visits to TSS and/or contractor's site, under the following terms:

- Site visits will be with reasonable notice and scheduling to accommodate parties.
- Site visits will be for the purpose of auditing the contractor's and TSS compliance with TCGA, NCI and NIH policies, and/or with contractor's and TSS own protocols provided to NCI under this work.

#### **2.1.1.2 IRB review, IRB protocol and Informed Consent**

The contractor and all TSS providing biospecimens and data to TCGA shall provide written documentation to the NCI Contracting Officer's Technical Representative (COTR) that an IRB has reviewed and approved participation. Such approval includes the cases when an IRB does not consider the work to be human subjects research (e.g. if participants are deceased) or considers the work to be exempt – documentation of these IRB positions is still required.

In addition, the contractor and all TSS must adhere to the following informed consent requirements:

- Patients shall give, or have given, informed consent for collection of the cancer and normal samples with genetic and/or genomic research being specifically permitted.
- The contractor and all TSS shall provide documentation of donor-specific date of consent and/or date of death for all cases.

In the case of new prospective collection protocols initiated in support of this work, each the contractor and all TSS shall provide copies of IRB protocols, IRB approvals, and the currently in use informed consent form.

### **2.1.1.3 Data Use Agreement**

Biospecimens and data shall be provided to TCGA under a Data Use Agreement that is in compliance with Health Insurance Portability and Accountability Act (HIPAA) Limited Data Set requirements (as of August 2009). Additionally, biospecimens and data shall be provided without any requirements for delayed use, delayed publication, review, or periods of data exclusivity for any party, with respect to the biospecimens and data provided or to the research data resulting from use of the biospecimens and data. Should applicable HIPAA regulations be modified over the term of this work, Contractor shall make necessary changes in contracts and Standard Operating Procedures (SOPs) to remain in compliance.

### **2.1.1.4 No automatic guest authorship**

Biospecimens and data provided to TCGA shall be free of any automatic requirement to include TSS investigators or other staff as authors on publications, merely by virtue of those individuals being TCGA tissue and data providers or affiliated with a TCGA TSS.

### **2.1.1.5 Intellectual Property**

Biospecimens and associated data shall be provided to TCGA free of any intellectual property encumbrances. Contractor Intellectual Property rights shall be governed exclusively by FAR 52.227-14, Rights in Data – General and as stated within this contract.

### **2.1.1.6 Material Transfer Agreement**

Many of the above requirements of this policy section are embedded in Material Transfer Agreements (MTA). TSS managed under this work (and other relevant parties) shall enter into an MTA with one of TCGA's BCRs, and the MTA shall meet the following requirements:

- A copy of the executed MTA, with signatures, shall be given to NCI to be deposited in TCGA's document repository.
- The NCI is not party to the MTA.
- The MTA terms shall include the following:
  - MATERIAL shall be defined to include both the physical biospecimens and the associated annotation data.
  - MATERIAL is for research use only, i.e., not for treatment, transplant, or diagnosis.
  - All parties shall comply with relevant laws.
  - PROVIDER does not retain intellectual property reach through rights to datasets generated with MATERIALS or DERIVATIVES or to future discoveries arising from those datasets.
  - Terms shall not differentiate between nonprofit and for-profit entities being part of TCGA's operations or data generating networks.

- Terms shall not differentiate between nonprofit and for-profit entity access to datasets.
- RECIPIENT is the custodian of the MATERIAL and acquires no ownership or intellectual property rights in the MATERIAL, derivatives, or future discoveries.
- At the end of the project, MATERIAL and derivatives shall be disposed of under the direction of the NCI.
- MTA shall pre-authorize the BCR to redistribute MATERIAL and DERIVATIVES to the various centers associated with TCGA.
- Regarding associated annotation data, MTA terms shall include:
  - A requirement that incoming data from TSS shall be compliant with HIPAA-defined “Limited Data Set” with the expectation that date/timestamp and geographical data will be included. PROVIDER shall warrant that data are in compliance.
  - Language for a HIPAA-compliant “Data Use Agreement” shall be included. The data use agreement shall pre-authorize the BCR to further transmit “Limited Data Set” compliant data to TCGA Data Coordinating Centers (DCC) under an appropriate Data Use Agreement (DUA).
- MTA shall require that the RECIPIENT not attempt to identify or contact MATERIAL donor or family members.

A template MTA for use in providing materials to a TCGA BCR is provided in Appendix A.

### **2.1.2 Specification of Cancers to be collected**

The Contractor shall provide cancer biospecimens, including, but not limited to, those provided in Appendix B. This list is preliminary, and is subject to having cancers added or eliminated. NCI may elect to approve the collection and banking of cancers not currently on the list.

NCI will make available to the Contractor the overall project objectives in terms of cancers to be studied and the general timelines for collection. This general information will be made available for information purposes only and shall not be used to begin significant cost-incurring operations for annotated biospecimen accrual for TCGA. This general information will be made available by providing contractor information from the relevant TCGA Steering Committee and sub-committee working groups on which TCGA planning and decision making occur. The contractor and the TSS shall incorporate this information in their tissue accrual plans.

### **2.1.3 Biospecimen requirements**

Contractor shall provide the following to NCI before the tissue samples are shipped to the BCR:

- Draft detailed Criteria for acquisition of biospecimens, including:
  - Physical and biological characteristics of tissues.
  - Number and timing of delivery of biospecimens required by TCGA.

- A list of cancer specific data elements that must accompany each case's set of biospecimens.
- Contractor shall initially draft above Criteria for each cancer. These draft Criteria shall be submitted to NCI for review and approval, and possible modification. If Criteria for a particular cancer type have already been developed by NCI, they will be provided to the Contractor. Draft criteria shall be due from Contractor within thirty (30) calendar days of notification from NCI that a particular cancer's collection should begin. Contractor shall note that some cancers will be initiated at time of contract execution, and others will start later in TCGA's schedule.
- NCI shall approve the final Criteria, which shall then be adopted by Contractor for operating the TSS network and biospecimen accrual.

The following sections describe the default criteria for TCGA biospecimens. The default criteria may change as the result of developing the Accrual Plan or during the course of TCGA based upon scientific or technology changes. Such change management shall be addressed in the project management plan (below).

#### **2.1.3.1 Biospecimen criteria for TCGA**

The contractor and all TSS networks shall provide per-case biospecimen sets that meet the following criteria :

- Both tumor tissue and a source of germline DNA (blood or component, DNA, and/or adjacent normal tissue) samples shall be available for every case.
- Primary tumor samples:
  - Derived from patients with a primary, untreated malignancy.
  - Snap-frozen to -86 deg C or colder
  - Sufficient tissue to yield 20 ug of co-isolated DNA and RNA (this is typically 150 – 200 mg of tissue).
  - Secondary tumors are excluded.
  - Optionally, neoadjuvantly treated recurrent tumors and/or metastases are requested, but only when case-matched with a primary, untreated specimen.
  - The time from cutoff of in vivo blood supply (devascularization) to ex vivo stabilization (freezing) shall be within 60 minutes; however 30 minutes or less is preferred.
  - A case-matched representative FFPE H&E section, or whole slide H&E stained digital image of section, from the original anatomic pathology diagnostic block of the tumor, confirmatory of the cancer.
  - Cellular composition of tumor sample shall be known or can be determined. By default for any cancer, the following tissue cellular composition cutoff values shall be used. Note, however, that cancer-specific values are subject to change at the discretion of the NCI, as dictated by TCGA goals and technological requirements.

- Each tumor sample shall be composed predominantly of histologically viable appearing tumor cells
  - Of viable cell nuclei present, on average,  $\geq 80\%$  shall be tumor nuclei.
  - $\leq 20\%$  of viable cells present may be normal stromal, inflammatory or immune cells
  - If necrosis is present, it may comprise no more than 20% of sample volume.
- Normal tissue:
  - Blood or blood component, a frozen sample of normal tissue, or both from the same patient shall be available for each case for purpose of obtaining germline DNA. In order of preference, the following are suitable: whole blood, PBL, purified DNA, other normal solid tissue.
  - The sample shall be sufficient to yield at least 20 micrograms of DNA.
  - If previously extracted DNA is provided, 20 micrograms shall be prepared. Assuming a normal white blood cell count and optimal cell recovery techniques, one 10-ml tube of blood is sufficient for recovery of 20- $\mu$ g of DNA, the optimal amount for TCGA analyses. If the white count is low or the cell recovery techniques sub-optimal, more blood may be required. Collection tube types, in descending order of preference are:
    - Yellow-top tube (Becton-Dickinson CPT, sodium citrate)
    - Blue-top tube (Sodium citrate)
    - Green-top tube (Heparin based tube)
    - Purple-top tube (EDTA) or red/black tiger-top tube (EDTA)
- Tumor biospecimens shall be prescreened by the contractor and all TSS to meet TCGA specifications. Prescreening shall be performed on a single section taken directly adjacent to one surface of the frozen candidate sample that would be sent to BCR. Any samples containing tumor within 10% of the cutoff value shall be submitted, as determined by review of a single section from one surface of the frozen material. Standard Operating Protocols for this process are in Appendix C.

Cancer-specific biospecimen requirements shall be developed over the course of TCGA, and shall result in deviation from the above defaults. These deviations may not be known at the time of contract award. Currently known deviations are listed by cancer in Appendix D.

## **2.1.4 Clinical and other data delivery requirements**

### **2.1.4.1 Data requirements for TCGA**

For each TCGA case of biospecimens provided to TCGA, the following data shall be provided:

- Original surgical pathology report, appropriately de-identified, to be submitted with the specimens.
- Biospecimen case control form, to be submitted with the specimens, which includes the documentation of informed consent and/or date of death.

- Tier 1, Tier 2 and Supplemental Case Report Forms (CRF) data, to be submitted once BCR has notified the contractor and the TSS that the specimens have passed relevant Quality Control steps.
  - For Tier 1: 100% of elements are required
  - For Tier 2 and Supplemental forms: >50% of form data elements are required for retrospective cases; 100% of form data elements are required for prospectively obtained cases.
  - Data shall be delivered within sixty (60) calendar days of BCR notification
- Follow-up / outcomes CRF at 6 month intervals, until either the patient is deceased or the term of the contract expires.
- Current TCGA generic and cancer specific data collection forms are in Appendix E.

## ***2.2 Requirements for Contractor's engagement with a TSS***

The Contractor's process for proposing an existing TSS, or establishing a new TSS, as a network site contributing biospecimens and data to TCGA shall include the following steps.

### **2.2.1 Identification of candidate Tissue Source Site(s) (TSS) with which to engage**

- Contractor shall identify to NCI candidate TSS for this work, including any already established networks of TSS to be used by the Contractor.
- Contractor may, at its discretion, choose to administratively and contractually aggregate multiple individual TSS into a single entity (e.g. a geographically dispersed hospital chain or multiple cancer collections within a single institution) if it makes bureaucratic, financial, and logistical sense to do so.
- Contractor shall be responsible for managing candidate TSS lists, and managing administrative data sufficient to report to NCI on status and progress of candidate TSS through this engagement process. Contractor shall keep this information current and be able to report to NCI at least weekly.

### **2.2.2 Review of candidate TSS(s)**

Contractor's detailed criteria for candidate TSS review shall be developed in conjunction with the NCI and approved by NCI. Contractor shall review candidate TSS according to:

- Availability of specimens (cancer, number and delivery timing) that meet the patient clinical, biospecimen and data requirements.
- Adherence to TCGA policy, administrative, and technical requirements for TSS participating in TCGA.
- Evaluation criteria that shall address the full breadth of characteristics relevant to biospecimen-based human subjects research, including:



- Ethical, Legal, and Policy issues, including patient re-contact and allowable use, compliance of collected samples and data with current laws, compliance of samples and data in accord with current accepted best ethical practices, and contractual status under MTAs.
- Clinical data quality, including availability of electronic records and ability to maintain contact with patients or their records in order to capture longitudinal information.
- Biospecimen annotation quality, including description of the collection process, physical characteristics, and management logistics.
- Biological quality, including histomorphological representativeness of the cancer, mass adequacy of individual samples, molecular integrity, and an estimate of the integrity of the biospecimens in terms of impact of collection and storage process on disease biology.
- Biorepository management quality, including the level of SOP detail under which the repository currently operates or operated when the biospecimens were collected.

### **2.2.3 Development of the Accrual Plan**

Upon final selection of TSS for tissue collection networks, Contractor shall deliver to NCI an Accrual Plan that includes estimates for retrospective and prospective:

- Number of cases worth of samples deliverable.
- Number of samples, sample types, and sample formats deliverable
- Timing for the completion of administrative documents.
- Timing for the availability of biospecimens.
- Timing for the availability of data.
- Issues that risk deviation from Contractor's pricing proposal.
- Risk assessment of factors that may significantly impact the above estimates, specifically including, but not limited to:
  - Risk to timing of sample and data availability
  - Risk of not meeting the case and sample numbers.
  - Risk of not being able to collect the minimum required clinical data.
  - Risk of not being able to complete administrative documents (human subjects approvals, MTA, DUA, etc.)
- Communication Plan that describes the interactions and reporting between TSS, Contractor, and NCI.

### **2.2.4 Approval of candidate TSS**

NCI will review the Accrual Plan and approve/disapprove the initiation of Contractor activities to include a candidate TSS as an operating TSS for TCGA.

## **2.2.5 Operations of biospecimen accrual at TSS**

NCI does not get involved in this beyond stipulating the biological requirements for the biospecimens and content requirements of the data. However, the NCI has extensive SOPs in this domain, and can require them, suggest them, and/or provide them as needed to the contractor.

## **2.2.6 Delivery of biospecimen and data from TSS to BCR**

The following requirements govern the delivery of biospecimens and data from TSS Network members to the BCR:

- Contractor shall not actually handle biospecimens/data or otherwise be directly involved the operations of shipment of materials and data from TSS to a TCGA Biospecimen Core Resource (BCR).
- SOP, logistics, training and other requirements for shipment of biospecimens and data from TSS to BCR shall be provided by BCR, and shall be abided by TSS.
- Contractor shall collect all necessary data to be able to report, at regular intervals and upon request, to NCI on the planned and actual number and timing of cases, specimens, and data delivery to BCR, and to report TSS performance against the Accrual Plan.

## **2.2.7 Ongoing operations**

- Contractor shall be responsible for obtaining from TSS information allowing Contractor to report on TSS actual performance against the Accrual Plan.
  - Contractor shall evaluate each TSS's performance against the accrual plan once 75 cases worth of biospecimens have been received, processed and quality controlled by BCR.
  - Contractor shall report weekly on TSS inventory numbers, accrual rates, cases shipped and estimated cases remaining. Contractor shall estimate expected cases to ship for the coming two (2) month period.
  - In the event of TSS non-performance against the Accrual Plan, the Contractor shall notify the Contracting Officer as soon as performance starts to decline or when there are performance issues.

## **2.3 Requirements of the Contractor**

### **2.3.1 Quality Management Plan**

The contractor shall adhere to its Quality Management Plan and shall notify the Government in writing of any changes to plan. The Quality Management Plan shall outline quality assurance and quality control policies and procedures to be used by the Contractor in the management of TSS network. This Contractor shall demonstrate an ability to interface with the Quality Management Program to be established by the TCGA.

### **2.3.2 Biospecimen collection protocols**

All prospective TSS collection protocols shall be governed by SOP, including, but not necessarily limited to:

- Human subjects protocols
- Tissue collection protocols
- Tissue handling and storage protocols
- Data collection protocols

All protocols shall be provided to NCI. Confidential protocols shall be marked as such. Protocols shall be reviewed for compliance with the TCGA goals and objectives, NCI's Best Practices for Biospecimen Resources, and against existing SOPs used by NCI Programs. Identified gaps will be communicated to the Contractor, and existing relevant SOPs will be shared with the Contractor. The Contractor shall modify existing protocols to incorporate the Government's comments. The Contractor shall routinely review the status of SOP use throughout the network of TSS. The Contractor shall report on status of SOP usage (compliance or breach) to NCI on a regular basis. Should breaches in SOPs be identified, the Contractor shall identify any risks to patients and to sample or data integrity and describe steps taken to avoid such breaches in the future. Should SOP breaches be demonstrably linked to poor specimen quality, the contractor and the TSS shall provide acceptable replacement specimens at no additional cost to the Government.

## **3 Individual Tissue Sites**

Individual clinical sites: This SOW covers the management of multiple individual Tissue Source Sites (i.e. networks). Individual Tissue Source Sites can be used if those sites meet one of two specific concerns:

- Site has a high potential rate of participant enrollment and specimen accrual (and/or extensive retrospective banks).
- Site can enroll participants and collect biospecimens from rare cancers (i.e. the cancers on the list in Appendix B).

## **4 Payment schedule for biospecimens and data**

A case is defined as all of the components identified in Payments 1 – 4. For TCGA designated cases, NCI will make fractional payments on the total per case price according to the following milestones:

- Payment 1 (25% of the total fixed price per case): Upon enrollment of the participant; banking of the tissue specimens; histological pre-screen of primary tumor specimen; delivery of tumor and normal specimens to BCR; and delivery of surgical pathology report and case control forms to BCR.
- Payment 2 (25% of the total fixed price per case): Upon the case's biospecimens passing BCR pathology and molecular QC steps. The Government will only pay for samples that pass QC.
- Payment 3 (25% of the total fixed price per case): Upon delivery of Tier 1, Tier 2 and Supplemental data case report forms to BCR with 45 days of being notified that a case's biospecimens have passed BCR QC. Contractors will be required to provide a refund or replacement case if these data cannot be provided.
- Payment 4 (25% of the total fixed price per case): Upon delivery of every 6 month follow-up case report form data to BCR until either the patient is deceased or the end of the contract.
- Additional payment: An additional payment of 20% of the fixed price will be made for recurrent and metastatic specimens and data case-matched to the samples provided in Payment 1 above. Such samples shall only be provided upon specific request from NCI.

## 5 Existing Networks

- Enumeration of any existing network(s) that the contractor has already established and that are currently in operation. Include:
  - Listing of TSS, business type, and geographic location.
  - Age of relationship with Offeror.
- Description of experience in establishing biospecimen accrual networks.
- Projected starting number and 1 & 2 year number of cases by cancer and timing of delivery of those case's biospecimens and data, in the following two categories:
  - Retrospective and Prospective biospecimen availability of cases mapped against the list of cancers provided in Appendix B.
  - Same as above, but additionally broken down to indicate the number of cases that would be accrued from already existing Contractor TSS relationships vs. new TSS relationships that Contractor proposes to establish.
- List and description of the contractor's own current criteria for engaging with TSS, in the following categories:
  - Human subjects protection, including IRB protocols and informed consent
  - Intellectual property
  - Biospecimen types (e.g. flash frozen, blood, FFPE), formats (e.g. OCT, cryovial) and stabilization parameters.
  - Clinical data elements collected, including any data elements related to patient follow-up
  - Geographical restrictions
  - SOP Offeror uses and deploys to TSS in its network

## **Appendices**

Appendix A: Material Transfer Agreement (template)

Appendix B: List of cancers

Appendix C: SOP for prescreen of biospecimens

Appendix D: Cancer-specific biospecimen composition deviations currently known

Appendix E: Generic Data collection forms

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## Appendix A: Material Transfer Agreement template

### **The Cancer Genome Atlas Project (TCGA) Material Transfer and Data Use Agreement**

#### ***For Transfers to the TCGA Biospecimen Core Resource (BCR) from organizations providing human biospecimens***

This Agreement is by and between \_\_\_\_\_ <insert name of institution providing biospecimens > (“Provider”) and \_\_\_\_\_ <insert name of institution receiving biospecimens> (“Recipient”) regarding the transfer of human specimens and associated data to the Recipient as part of The Cancer Genome Atlas (TCGA) project. Provider and Recipient are collectively referred to as the “Parties.”

WHEREAS, in order to improve the ability to diagnose, treat, and prevent cancer, the National Cancer Institute (“NCI”) and the National Human Genome Research Institute (“NHGRI”), member institutes of the National Institutes of Health, an agency of the federal government, have jointly undertaken the TCGA -project as a comprehensive and coordinated research effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing;

WHEREAS, the major organizational components of the TCGA are the TCGA Human Cancer Biospecimen Core Resource (“BCR”), the TCGA Genome Characterization Centers, the TCGA Genome Data Analysis Centers and TCGA Genome Sequencing Centers, which are third party institutions funded, respectively by the NCI and the NHGRI (collectively the “Centers”), and the TCGA Data Coordination Center (“DCC”), which is operated by NCI through the NCI Center for Bioinformatics;

WHEREAS, the purpose of the TCGA BCR is to minimize the variability introduced by the collection, processing and handling of selected human biospecimens and derivative materials that will be studied during the course of the TCGA project;

WHEREAS, Provider, a covered entity subject to the Health Insurance Portability and Accountability Act of 1996, as amended, and accompanying regulations, intends to transfer a set of human biospecimens and associated data to Recipient;

WHEREAS, Recipient is funded to operate as the TCGA BCR under a contract to receive, process and distribute human biospecimens, derivative materials and associated data to the TCGA Centers;

WHEREAS, Recipient, will receive, process and distribute biospecimens received from Provider, materials derived from such biospecimens, and associated data to the TCGA Centers;

WHEREAS, Provider and Recipient desire to protect the privacy and provide for the security of certain information disclosed to Recipient in compliance with HIPAA and other applicable laws and regulations,

NOW, THEREFORE, in consideration of the mutual promises in this Agreement and for other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties hereby agree as follows:

1. **DEFINITIONS.** Within this Agreement, the following terms will have the same meaning as those used in the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 CFR Parts 160 and 164 (“HIPAA Privacy Rule. These terms are repeated here for convenience.

(a) Under 45 CFR 164.500 (“Applicability”), a “covered entity” is an organization, individual, institution, or other entity that is subject to the standards, requirements, and implementation specifications of the HIPAA Privacy Rule with respect to protected health information under.

(b) Under 45 CFR 164.514 (“Other requirements relating to uses and disclosures of protected health information”), “De-identified” information is information that formerly contained individually identifiable health information, but which has had all unique identifying information, numbers, characteristics, and codes removed such that the information a record contains cannot be used alone or in combination with other information to identify the individual who is the subject of the information. Identifying information includes, but is not limited to, the 18 categories of identifiers described in 45 CFR 164.514(b)(2).

(c) Under 45 CFR 164.501 (“Definitions”), “Protected Health Information” or “PHI” means any information, whether oral or recorded in any form or medium: (i) that relates to the past, present, or future physical or mental condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual, and (ii) that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

(d) Under 45 CFR 164.514(e) (“Implementation Specification: Limited data set”), a “limited data set” (herein “LDS”) is protected health information that excludes the 15 specific direct identifiers listed in that section. Any such identifying information that identifies the individual who is the subject of the PHI, his or her relatives, employers, or household members must be removed for the PHI to constitute an LDS. Unlike de-identified PHI, and LDS *may* contain postal address information, including a town, city, State, or zip code; specific dates, for example, dates of birth, admission, treatment, or release; and any other information, not specifically listed in that section, that could be used alone or in combination with other information to identify a specific individual.

## 2. DESCRIPTION OF MATERIAL AND DATA.

(a) The material to be transferred (“ORIGINAL MATERIAL”) is a set of human biospecimens described specifically as:

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(b) The data to be transferred to Recipient are clinical, biological, technical or other information describing the ORIGINAL MATERIAL specimens (“DATA”). Some of the DATA may be PHI. DATA, regardless of whether or not it is PHI regulated by HIPAA, will be transferred in a form technically compliant with an LDS. The DATA may include the following data elements: dates; timestamps; ages; dates of birth, death, admission and discharge; dates of service; and geographical information, including zip codes or any other geographic subdivisions.

**3. COLLECTION OF MATERIAL AND DATA.** The ORIGINAL MATERIAL and DATA have been collected by Provider under an Institutional Review Board (“IRB”) approved protocol, including all necessary informed consents, and authorizations, which disclose potential redistributions of the ORIGINAL MATERIAL or materials derived from the ORIGINAL MATERIAL, e.g., DNA and RNA products (“DERIVATIVE MATERIAL”) (ORIGINAL and DERIVATIVE MATERIAL are collectively referred to as “MATERIAL”) and DATA, in accordance with Section 4 of this Agreement, in compliance with all applicable laws, regulations and policies for the protection of human subjects, including 45 CFR Part 46, “Protection of Human Subjects” (the “Common Rule”), the HIPAA Privacy Rule, and any necessary approvals, authorizations, human subjects assurances, informed consent documents, and IRB approvals.

**4. TRANSFER OF ORIGINAL MATERIAL AND DATA; PURPOSE.** Provider agrees to provide the ORIGINAL MATERIAL and DATA in accordance with applicable laws, regulations and policies, including the Common Rule, the HIPAA Privacy Rule, and any necessary authorizations, human subjects assurances, informed consent documents, and IRB approvals. Provider will remove any elements of the 15 LDS-specific direct identifiers from the DATA before transfer to Recipient. The sole purpose of the Provider’s transfer of the DATA to Recipient is to enable Recipient to receive, process and distribute the ORIGINAL and DERIVATIVE MATERIALS and DATA to the TCGA Centers and the TCGA DCC at NCI in fulfillment of its contractual obligations to NCI’s OTS contractor (“Purpose”).

(a) Provider hereby grants Recipient explicit permission to further distribute the MATERIAL and DE-IDENTIFIED DATA to the TCGA Centers.

(b) Provider hereby grants Recipient explicit permission to further distribute the DATA to the TCGA DCC located at the NCI upon execution between Recipient and NCI of a data use agreement that is consistent with the terms of this agreement. Furthermore, Provider acknowledges and agrees that Recipient may allow the TCGA DCC to provide all or part of the DATA to third parties under separate data use agreements that are no less restrictive than this Agreement and that prohibits such third parties from further distributing the LDS.

#### **5. RESPONSIBILITIES AND AUTHORIZATIONS OF RECIPIENT**

(a) Recipient is authorized to receive the ORIGINAL MATERIAL AND DATA under an IRB approved protocol or IRB granted waiver. Recipient agrees to handle and distribute the MATERIAL in accordance with all applicable laws, regulations and policies, including, as applicable, the Common Rule, the HIPAA Privacy Rule, and any necessary human subjects assurances, informed consents and IRB approvals.

(b) Recipient is not authorized and shall not further disclose the DATA other than as permitted by this Agreement or as otherwise required by law. Recipient shall not distribute the DATA to other third parties without written consent from Provider and NCI’s Contracting Officer.

(c) Recipient shall use appropriate administrative, technical, and physical safeguards to prevent use or disclosure of the DATA other than as provided for in this Agreement.

(d) Recipient shall notify Provider in writing within five (5) working days of its discovery of any use or disclosure of the DATA not permitted by this Agreement of which Recipient, its officers, employees, or agents become aware. Recipient shall take (i) prompt corrective action to cure any deficiencies or (ii) any action pertaining to such unauthorized disclosure required by applicable federal law.



(e) Recipient shall ensure that any of its agents or subcontractors agrees with Recipient in writing that such agent or subcontractor will hold any DATA transmitted from the Recipient to such agent or subcontractor confidential and will use or disclose the DATA only for the purpose for which it was used or disclosed to the agent or subcontractor, or as required by law. Additionally, the agent or subcontractor shall notify Recipient of any instances, of which it is aware, in which the Information has been used or disclosed inconsistent with this Agreement.

(f) Recipient agrees to not identify or contact any donor or living relative who is associated with the MATERIAL or any DATA received under this Agreement from Provider. Furthermore, Recipient will not attempt to obtain or otherwise acquire any DATA associated with the MATERIAL beyond that which is provided by the Provider.

(h) Recipient will retain and abide by this Agreement for as long as it retains DATA received from the Provider plus 6 (six) years after the date it returns or destroys all such information.

**6. BREACH OR VIOLATION.** Provider is not responsible for Recipient's violations of this Agreement, unless Provider knows of a pattern of activity or practice that constitutes a material breach or violation of this Agreement, in which case it must take reasonable steps to cure the breach, end the violation or withhold the DATA delivered to Recipient.

**7. THE MATERIAL AND DATA ARE NOT FOR USE IN HUMAN SUBJECTS OR FOR THE TREATMENT OR DIAGNOSIS OF HUMAN SUBJECTS.**

**8. DISCLAIMER.** Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. SUBJECT TO THE REPRESENTATIONS IN SECTION THREE (3) ABOVE WITH RESPECT TO THE MATERIAL OR DATA, PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL OR DATA WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. To the extent allowed by law, Recipient assumes liability for claims for damages against it by third parties which may arise from its use, storage, processing, distribution or disposal of the MATERIAL except that, to the extent permitted by law, Provider shall be liable to Recipient when the damage is caused by the gross negligence or willful misconduct of Provider.

**9. DISPOSAL OF MATERIAL AND DATA.** At the end of its contract with NCI, Recipient will dispose of the MATERIAL and DATA in the manner decided at the sole discretion of NCI and consistent with law and the informed consent of the individual providing the ORIGINAL MATERIAL. Such disposition on behalf of NCI may include, but is not limited to, continued storage on behalf of NCI for future research, return to Provider, transfer to the NCI, use in an expansion of TCGA, transfer to another organization acting on NCI's behalf, or destruction.

**10. INTELLECTUAL PROPERTY.** Provider acknowledges and agrees that it does not by virtue of this Agreement acquire any intellectual property rights in the future inventions or discoveries made by third parties using the MATERIAL or DATA distributed by Recipient. Recipient acknowledges that it serves only as the custodian of the MATERIAL and DATA, and therefore agrees that it does not by virtue of this Agreement acquire any intellectual property rights in the MATERIAL, nor any future intellectual property rights in any research conducted by third-parties using the MATERIAL or DATA.

**SIGNATURES**

\_\_\_\_\_

\_\_\_\_\_

Signing Official

Date

\_\_\_\_\_

Name of institution providing biospecimens

\_\_\_\_\_

\_\_\_\_\_

Signing Official

Date

\_\_\_\_\_

Name of institution receiving biospecimens

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Appendix B: List of cancers (subject to change)

Sites
Glioblastoma multiforme
Lung squamous cell carcinoma
Breast ductal carcinoma
Colon adenocarcinoma
Breast lobular carcinoma
Lung Adenocarcinoma
Stomach adenocarcinoma
Hepatocellular carcinoma
Head and neck (oral) squamous cell carcinoma
Pancreatic ductal adenocarcinoma
Uterine Corpus (endometrial carcinoma)
Astrocytoma
Cutaneous melanoma
Renal cell carcinoma
Prostate adenocarcinoma
Kidney Papillary Carcinoma
Cervical Cancer (squamous)
Bladder urothelial carcinoma – nonpapillary
Bladder urothelia carcinoma – papillary
Thyroid follicular carcinoma
Thyroid papillary carcinoma
Non-Hodgkins Lymphoma (ex Diffuse large B-cell lymphoma)
Acute Myeloid Leukemia
Chronic Lymphocytic Leukemia
Multiple Myeloma
Diffuse large B-cell lymphoma
Other Cancer Type Currently Not Identified

## ***TSS Preparation of Top Slides Working Instructions***

The contractor and the TSS shall ensure that the TSS preparation of all top slides follows the below instructions/procedures.

### **I. Purpose:**

The purpose of this instruction is to establish a procedure for obtaining a section of unfixed frozen tissue for a “top” slide.

Frozen tumor samples shall be submitted by Tissue Source Sites (TSS) to the Biospecimen Core Resource (BCR) for consideration in TCGA. Prior to submission of those tissues the histology department of the TSS shall create one top slide, one at either end of the tissue sample and stains the slide with hemotoxylin and eosin. Each top slide shall be reviewed by a board certified pathologist at the TSS to evaluate tissue samples for submission to the BCR that meet inclusion requirements as evaluated by the pre-defined pathology qualification acceptance criteria for the project.

To ensure inclusion requirements contribution into the TCGA project, the contractor and the TSS shall verify that the following sample qualifying criteria are met:

- Both tumor and normal samples are available;
- Tumor sample size:  $\geq 200$ mg in weight;
- Tumor samples shall be comprised of  $\geq 80\%$  tumor nuclei;
- The tissue shall be comprised of  $\leq 20\%$  necrosis ( $\leq 50\%$  necrosis for GBM);
- Tumor samples shall be snap frozen and derived from patients with a primary, untreated malignancy;
- A frozen sample of normal tissue/blood from the same patient shall be available for each case. Extracted DNA (minimum of 13  $\mu$ g) from patient blood or other normal tissue sample is also acceptable;
- Cellular composition of tumor sample is known or can be determined.
- Access to associated sample clinical data shall be available.

### **II. Procedure:**

1. Ensure all utensils have been cleaned with 70% ethanol prior to placing in the cryostat and/or dry ice container.
2. Carefully remove frozen tissue samples from the storage cryofreezer and immediately transfer the sample(s) to a container of dry ice that is large enough to allow all samples to be kept completely frozen during the procedure of obtaining ‘top’ slides. **Ensure that the samples are kept cold with dry ice at all times.** If the

frozen tissue sample is not on dry ice, it must be inside a cryostat, a -80°C freezer or a cryofreezer.

3. Carefully remove the sample from its container with sterilized forceps and place it in a pre-chilled Petri dish on dry ice. When extracting the frozen tissue sample from its container, take extra care not to force the forceps through the container or tissue sample.

**It is imperative that the tissue sample not be exposed to conditions that would promote thawing during this procedure.**

4. **Be certain that the cryostat hand-wheel is in the locked position.** The frozen tissue sample, in the pre-chilled Petri dish on dry ice, will be transferred to a weigh boat using sterilized forceps. The weigh boat containing the frozen tissue sample will be immediately placed in the cryostat. Place an appropriate amount of OCT mounting medium on to the specimen disc and adhere the frozen tissue sample to the liquid OCT. Work quickly to ensure the tissue contains OCT before the medium freezes.
5. After the OCT has solidified, place the specimen disc onto the specimen head of the cryostat and tighten. Adjust the angle of the specimen head to ensure that a complete represented section of tissue will be obtained for the 'top' slide.
6. Place a clean, disposable blade into the blade holder and tighten.
7. Using proper cutting technique (refer to the cryostat manufacturer's microtomy procedure) face into the frozen tissue to expose the surface.
8. Obtain a 4 - 5 micron section and place on a blue glass slide. Blue slides represent 'top' to the BCR, however, any color of slide that is available to the TSS is acceptable. Ensure that the slide is properly labeled (using a Statmark pen) with the TSS number, (if applicable) the slide procurement date (e.g., 18 Jan 08) and the word 'top'.
9. **Be certain that the cryostat hand-wheel is in the locked position.** Remove the specimen disc from the specimen head of the microtome and place upside down (i.e. tissue facing down) in the dry ice.
10. To remove the frozen tissue from the "specimen disc", grip the base of the OCT with sterilized serrated tip forceps and twist for a clean breakaway of the frozen tissue sample containing OCT.
11. After the frozen tissue sample containing OCT is separated from the specimen disc, obtain a pre-chilled sample container that is large enough to allow space for the frozen tissue sample to be placed into it with the attached OCT surrounding it. A list of these sample containers include but are not limited to:
  - Plastic contact lens cases that have been snapped in half,
  - Aluminum foil,
  - Plastic embedding molds,
  - Tissue cassettes,
  - 50ml conical tubes,
  - Cryovials – ensuring OCT is NOT surrounding frozen tissue sample.
12. **At no time should the frozen tissue sample containing OCT be subjected to thawing conditions in order to fit into a sample container. A sample container**

**must be obtained that will allow for the size of the frozen tissue sample with the OCT attached to fit into and maintain its original shape.**

13. Ensure that the TSS sample identification number is clearly visible on the sample container. Materials for TSS sample identification writing include: using a Sharpie® on tape to attach to the aluminum foil or for labeling the plastic contact lens cases and using a Statmark pen or pencil for labeling tissue cassettes, conical tubes or cryovials. Ensure that any label that is used for the purpose of the TCGA project is capable of withstanding the extreme temperatures associated with a cryofreezer, a -80°C freezer, a cryostat or a cryoport.
14. Place frozen tissue sample containing OCT in a labeled sample container on dry ice large enough to accommodate a cardboard box for sample shipping.
15. Clean all utensils with 70% ethanol prior to starting new frozen tissue sample.
16. Obtain a new sterile Petri dish for the next frozen tissue sample. The used Petri dish must be discarded in the biohazard waste.
17. Obtain a new weigh boat for the next frozen tissue sample. The used weigh boat must be discarded in the biohazard waste.
18. Obtain a new blade for sectioning the next frozen tissue sample 'top' slide on the cryostat. Discard the used blade into a biohazard sharps container.
19. It is recommended for optimum quality control that a second person match the TSS number of the sample to the number on the sample container and to verify that the correct TSS number is on the 'top' slide. These steps should be performed prior to H & E staining.
20. Once all the frozen tissue samples that have been sectioned for the 'top' slide are placed into their appropriate sample containers (i.e. the container that the frozen tissue sample will be shipped to the BCR in) and are in the cardboard storage box, it is necessary to then place the box of samples into a cryofreezer for storage until shipment to the BCR.
21. Stain 'top' slides using hematoxylin and eosin.
22. If a frozen tissue sample is in more than one piece and is from the same patient and tumor, it is imperative that the pieces be identified separately by being placed into individual sample containers and has a 'top' slide sectioned to represent each piece. If the TSS chooses to place the pieces into the same sample container for shipping to the BCR, each individual frozen tissue piece must be oriented with a small dab of tissue marking ink to assist the BCR on which end of the frozen tissue sample the section came from. Alternatively, you may aggregate the frozen tissue pieces and embed them together in OCT to obtain one representative section from all the tissue pieces.

### **III. Safety:**

- Wear personal protective equipment (PPE) such as lab coats, nitrile or latex gloves, eye goggles or face shield and close-toed shoes.
- Bloodborne pathogens can be present in the unfixed frozen tissue, use universal precautions.

- Liquid nitrogen is extremely cold and can cause ‘burns’. Wear gloves that are specially made to withstand liquid nitrogen, eye protection and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.

#### **IV. References: Equipment, Materials and Quality Control**

##### **Equipment and Materials:**

- Cryostat
- Specimen discs compatible with the cryostats in use at the TSS.
- Optimal Cutting Temperature Medium (OCT, Lung Tissue Media-020108926)
- Shandon low profile microtome blades
- Serrated tip forceps (Fisher Scientific, Cat # 1381214)
- 100 mm sterile Petri dishes or tissue culture dishes (Falcon, or similar)
- Dry ice
- 1 insulated bucket for dry ice (Styrofoam or plastic)
- Frozen tumor tissue
- 4x4 gauze
- Nitrile/Latex gloves
- 70% Ethanol
- Blue frosted glass slides (Unimark)
- Statmark pen for slide identification (Cat # SMP-BK)
- Cardboard box specific for storage of cryovials and/or tissue samples

**It is possible to substitute materials and certain equipment from other vendors as long as they are the equivalent of the item described above.**

**Products and disposable materials used need to be RNase-free, and handled only with gloved hands in order to prevent contamination with skin RNases.**

**All reagents must be made with RNase-free materials and chemicals, and containers and tubes with samples must be kept covered when possible during the entire procedure to ensure they remain dust and RNase-free. In the case that a reagent or disposable becomes contaminated, it must be discarded.**

##### **Quality Control:**

- The frozen tissue sample must remain frozen throughout the entire procedure of obtaining a ‘top’ slide for the BCR. To ensure this always work with frozen tissue samples either inside a cryostat or in a container of dry ice.
- For optimum quality control, it is recommended that each frozen tissue sample be handled in teams of two histologists; each individual being proactive in sample

identification, labeling of slides with the sample identification number and returning of frozen tissue sample to the cryofreezer prior to shipping to the BCR.

- All sample labels shall be visually inspected by both individuals to ensure that the sample is being placed in an appropriately labeled vial.
- The cryostat shall be checked prior to beginning any work to make sure it is in good working order (i.e., able to rotate one full rotation).
- Avoid tissue loss during the sectioning procedure. When creating sections, face the frozen tissue sample that is within OCT, removing only the quantity of tissue required to expose the surface.

### ***TSS Pathology Prescreen Review of Tissue Specimen Top Slide Working Instructions***

The contractor and the TSS shall ensure that the TSS pathology prescreen review of tissue specimen top slides follows the below instructions/procedures.

#### **I. Purpose**

The purpose of this working instruction is to establish a procedure for the Pathologist at the Tissue Source Site (TSS) to review biospecimen H&E slides and document pathology results. This procedure applies to all board-certified Pathologists as well as a board-certified Pathologist with specialized training.

Frozen tumor samples are submitted by TSS to the Biospecimen Core Resource for consideration in TCGA. Prior to submission of those tissues the histology department of the TSS creates one top slide, one at either end of the tissue sample and stains the slide with hemotoxylin and eosin. Each top slide is reviewed by a board certified pathologist at the TSS to evaluate tissue samples for submission to the BCR that meet the qualification metrics as evaluated by the pre-defined pathology control acceptance criteria for the project (see Qualification Acceptance Criteria).

Working instructions do not supersede any Department Policies or Standard Operating Procedures; however, are intended for training and consistency of daily operational functions for TCGA.

#### **II. Procedure: Working Instruction Compilation and Maintenance**

1. Review qualification acceptance criteria metrics for specimen consideration.
2. Document Tissue Source Site Tumor Slide Identifier on Case Quality Control Form.
3. Evaluate one newly created specimen top H & E slide per case utilizing appropriate pathology techniques to evaluate:



Confirmation of Diagnosis	Percent Necrosis*	Percent Tumor Nuclei*
• Glioblastoma Multiforme (GBM)	≤ 50%	≥ 80%
• Serous Cystadenocarcinoma	≤ 20%	≥ 70%
• Squamous Cell Carcinoma	≤ 20%	≥ 80%
*Note, submit specimens for evaluation within a 10% window of necrosis and nuclei metrics for consideration.		

4. **Confirmation of Diagnosis:** The original case diagnosis (pathology report) should be compared and confirmed against the specimen slide under evaluation for project submission.
5. Document the confirmed diagnosis on the Case Quality Control Form.
6. **Percent Necrosis:** The entire specimen field should be evaluated under low power (2x-4x) magnification to determine the percent of tissue necrosis present utilizing geographical specimen landmarks as a measurement guide.
7. After initial estimation of necrosis, confirm percent estimate under high power (10x-40x) magnification to validate the absence of nuclei.
8. Document the percent necrosis on the Case Quality Control Form.
9. **Percent Tumor Nuclei:** A minimum of ten specimen fields should be evaluated under high power magnification. Begin at 10x and magnify up to 40x to evaluate the percentage of tumor nuclei within the viable non-necrotic specimen area to determine a quantitative percent representation of the number of tumor nuclei present.
10. Note: If homogenous consistency exists throughout the sample the TSS pathologist must utilize professional judgment to increase the number of fields assessed to grade the percentage of tumor nuclei.
11. Document the percent tumor nuclei on the Case Quality Control Form.
12. It is important to note that pathology interpretation may vary; therefore once diagnosis is confirmed, it is acceptable to submit any specimen within a 10% window of calculation for evaluation. For example, if case evaluation returns 70% tumor nuclei submit case to the BCR for project consideration.
13. Pathologist performing review signs Case Quality Control Form in section titled, "To Be Completed by Pathology."
14. Note: One form is to be completed per slide and submitted in plastic envelope with cryoport shipment to the BCR; see *Completion of Case Quality Control Form* instructions.
15. Prepare top slides for shipment to the BCR; see *Shipment of Top Slide* instructions.

### **III. Safety**

1. Glass slides can have sharp edges. Be careful while handling any glass component.
2. Bloodborne pathogens can be present in unfixed frozen tissue. Use universal personal protective equipment (PPE), such as lab coats and gloves when handling all specimens.

### **IV. References: Equipment, Materials and Quality Control**

#### **Equipment and Materials**

- Light microscope
- H&E slide(s) of samples to be reviewed and documented
- Case Quality Control Form (TCGA #A1.034v2)

#### **Quality Control:**

- Tissue Source Site slide identifier shall be verified against the slide number on TCGA Quality Control Form when slide is placed on the microscope stage to ensure the correct slide is being reviewed.

Appendix D: Tumor cellular composition deviations from default currently known

Glioblastoma multiforme

Necrosis composition on prescreen section: qualifying sample is  $\geq 40\%$

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## Appendix E: Data collection forms

See separately attached PDF documents

File name: The Cancer Genome Atlas forms – lung V 2 5 080829.pdf

File name: The Cancer Genome Atlas forms – ovary V 2.5 080829.pdf

File name: The Cancer Genome Atlas forms – GBM V 2.9 081001.pdf

### Generic

- Tier 1
- Tier 2
- Supplemental

### GBM

- Tier 1
- Tier 2
- Supplemental

### Lung

- Tier 1
- Tier 2
- Supplemental

### Breast

- Tier 1
- Tier 2
- Supplemental