

# The Cancer Genome Atlas Biospecimen Selection Process

## Executive Summary

The National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) initiated a 3-year pilot project, The Cancer Genome Atlas (TCGA) (<http://cancergenome.nih.gov>), to determine the feasibility of cataloging the genomic alterations associated with a set of human cancers. The overall aim of TCGA initiative is to accelerate the understanding of the molecular basis of cancer through the development and application of high resolution, high throughput genome analysis technologies in the study of human cancer biospecimens. The pilot project focuses on a several tumor types to assess the feasibility of conducting a comprehensive analysis of associated genomic alterations in the future in all cancer types. The pilot project will verify whether cancer-associated genes and/or genomic regions can be identified by combining information from genome analyses with tumor biology and clinical data and whether the sequencing of selected regions can be efficiently achieved. Collectively, genomic and clinical data generated by all the components of the pilot project will provide the initial contributions to a comprehensive Web-based resource describing the genomic “fingerprints” of specific cancer types.

TCGA comprises four major components: the Biospecimen Core Resource (BCR); the Cancer Genome Characterization Centers (CGCCs); the Genome Sequencing Centers (GSCs); and the Data Management, Bioinformatics and Computational Analysis Core. TCGA pilot project depends on high-quality biospecimens, and to that end, the BCR was established to act as the management unit to oversee biospecimen analysis, acquisition, processing, and biomolecules distribution with uniform quality standards to the GSCs and CGCCs.

This document describes the process of developing and applying the selection criteria used to evaluate suitable biospecimen collections for TCGA. This process ensures that participating TCGA laboratories uniformly receive the highest quality analytes that will enable them to generate high-quality and comparable data.

The NCI identified candidate biospecimen sources through a widely disseminated request for information (RFI). The list of possible sources was evaluated and chosen in a three-stage process described in this report. All the questions in the RFI and all the biospecimen selection criteria were developed with broad input from NCI and NHGRI staff members, extramural cancer researchers, and expert consultants. The process resulted in quantitative metrics of evaluation that were applied to all sources.

The last stage of the selection process included a review by the Biospecimen Expert Technical Panel that evaluated the information on the candidate biospecimen collections using the quantitative parameters and additional factors, including scientific relevance and burden of disease.

## Background and Introduction

In 2004 the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) convened a workshop to consider a project to identify as comprehensive a set of genetic changes in cancer as possible. A few months earlier, Dr. Andrew von Eschenbach, Director of the NCI, requested that a working group of the National Cancer Advisory Board (NCAB) evaluate the status of advanced technologies in the context of the NCI's 2015 challenge goal to eliminate suffering and death due to cancer. This working group presented a series of recommendations to the NCAB in February 2005 that included a genomic characterization and resequencing project that would be initiated through a pilot project and subsequently scaled up depending on the outcome of the first phase ([http://deainfo.nci.nih.gov/Advisory/ncab/sub-bt/NCABReport\\_Feb05.pdf](http://deainfo.nci.nih.gov/Advisory/ncab/sub-bt/NCABReport_Feb05.pdf)).

Based on the NCAB working group's recommendations and broad input from the scientific community, the NCI and the NHGRI agreed to support The Cancer Genome Atlas (TCGA) pilot project (<http://cancergenome.nih.gov/>). A joint staff-level planning and management structure for the project was established in March 2005. TCGA Management Team (TMT) has developed an overall approach and plan for the pilot project based on the NCAB Working Group Report on Biomedical Technology ([http://deainfo.nci.nih.gov/Advisory/ncab/sub-bt/NCABReport\\_Feb05.pdf](http://deainfo.nci.nih.gov/Advisory/ncab/sub-bt/NCABReport_Feb05.pdf)) and two workshops: "Exploring Cancer Through Genomic Sequence Comparisons" ([http://cgap.nci.nih.gov/Info/genomic\\_comparison](http://cgap.nci.nih.gov/Info/genomic_comparison)) and "Toward a Comprehensive Genomic Analysis of Cancer" ([http://cgap.nci.nih.gov/Info/TCGA\\_executive\\_summary.pdf](http://cgap.nci.nih.gov/Info/TCGA_executive_summary.pdf)). The overarching goal of the TCGA pilot project is to leverage the existing infrastructure, extant knowledge bases, and resources of the NCI and the NHGRI to conduct the high-throughput molecular analysis of cancer samples from highly defined and annotated human biospecimens of the highest quality.

A major requirement for TCGA pilot project is the analysis, acquisition, processing, and distribution of high-quality biospecimens. Therefore, the NCI supports the establishment of a Biospecimen Core Resource (BCR) to receive and manage quality-verified tissues with associated clinical annotation, isolate biomolecules from those tissues, qualify and perform a quality control (QC) review of biospecimens during the process, and aliquot and distribute those materials to TCGA Cancer Genome Characterization Centers (CGCCs) and Genome Sequencing Centers. The biospecimens will come from both retrospective collections and prospective collections. Standard operating procedures (SOPs) will be used for all steps, including informed consent, clinical data collection, sample collection, pathological examination, biomolecule extraction, QC, laboratory data collection, and biomolecule distribution.

The sources of BCR tissue biospecimens are biorepositories that have been identified by the TMT as a result of a response to an NCI-issued request for information (RFI). The biospecimen collections were identified, evaluated, and qualified to ensure that only the highest quality biospecimens are obtained by the BCR. It is important to note that "high quality" refers not only to biological quality of the samples (i.e., the histological and molecular state [the latter refers to the intactness of the biomolecules within the tissue]) but also to the status of ethical and legal documents associated with the samples and related clinical annotation (i.e., institutional review board [IRB] protocol review, appropriateness of the informed consent process, and presence or

availability of material transfer agreements [MTAs]), the quality of the associated data (i.e., the extent of donor clinical and biospecimen annotation), and the degree of process documentation (e.g., sample handling and storage protocol detail, quality assurance (QA), and QC).

The TMT established a three-stage process to evaluate biospecimen collections using a set of criteria that ensured that the samples collected and distributed by the BCR meet the necessary high-quality standards and the scientific goals of TCGA.

## **Biospecimen Selection Process**

The biospecimen selection process was developed and managed by the NCI's Office of Cancer Genomics (OCG) and approved by the TMT and Biospecimen Expert Technical Panel. The details of the development of the selection process are expanded in Appendix 1. A list of various groups' membership is provided in Appendix 2.

### **Goals and Overview**

The goals of the selection process were to ensure broad community input into the cancer biospecimen selection criteria, ensure that the selection criteria are applied to evaluate candidate biospecimen collections, and ultimately deliver high-quality biospecimens able to meet the ethical, legal, scientific, and technical needs of TCGA. A flowchart of the biospecimen source selection process is shown in Figure 1. The process began with identifying candidate biospecimen collections through the issuance of a Request for Information (RFI), attached as Appendix 3.

### **Request for Information**

The process began with identifying candidate biospecimen collections through the issuance of a RFI (Appendix 3). In fall 2005, the NCI issued a RFI to identify existing biorepositories that may contain sample collections suitable for TCGA and whose custodians would be willing to contribute those samples to the project. Responses were accepted and reviewed from any U.S. or foreign entity, both NCI-funded and non-NCI-funded resources, and commercial sources. The list of potential collections identified by the RFI was evaluated in three stages.

#### ***Purpose of the RFI***

The goal of the RFI was to elicit responses from all biorepositories with samples suitable for TCGA research. The RFI comprised questions designed to encourage responses from biorepositories that were formally established entities with significant ethical, technical, biological, pathologic, and bioinformatics resources. In addition, the RFI questions were designed to ensure that responses included sufficient information to evaluate them based on the requirements for the project.

The complete set of RFI responses was submitted to the evaluation process.

### **Primary Criteria**

The Primary Criteria are minimal qualification characteristics used to evaluate biospecimen collections on the basis of quality, quantity, and extensiveness of annotation of information relevant to the pilot project.

## **Primary Criteria Goals**

The goal of the Primary Criteria was to identify biospecimens that were of uniform high quality in all the areas relevant to TCGA requirements. These areas include the ethical and legal status of donors, their samples, and their data; the permission to reapproach the donors; the granularity and standardization of tissue collection and handling protocols; the quality of clinical annotation and likelihood of collecting longitudinal and outcome information; and the histological and biological quality of biospecimens. The Primary Criteria are listed in Appendix 5.

The Primary Criteria include evaluation of the following characteristics:

- Minimum quantity of appropriate samples. TCGA workshops have established that 500 samples from unique cases will be required for statistical power. These samples must include access to case-matched “normal” tissue sources, be of sufficient weight to yield both RNA and DNA, and be amenable to pathology review.
- Clinical trial. The donors should have been enrolled in a clinical trial, or equivalent, to ensure standardization of entry criteria, treatment, data collection, and follow up. If donors have not participated in a clinical trial (e.g., a molecular characterization study), the protocol requirements must include the aforementioned activities accomplished with the same rigor as in a clinical trial.
- Informed consent. The TMT established that donors must be recontacted before their samples can be used in TCGA because of the extensive genomic data being generated and posted on publicly accessible databases. The original collection consents must permit donor recontact, or the IRB must be willing to grant a waiver to permit recontact so that such concerns can be understood by donors.

The Primary Criteria represent a “yes” or “no” filter, against which candidate biospecimen collections must meet all requirements in order to be further considered for TCGA pilot project. Those candidate collections that passed the Primary Criteria proceeded for ranking with the Secondary Criteria.

## **Secondary Criteria**

The Secondary Criteria were used by the ETP in evaluating collections for TCGA and are provided in Appendix 6.

### **Secondary Criteria Goals**

The Secondary Criteria were used to provide qualitative and quantitative measures of the biospecimen characteristics to facilitate prioritization of the sample selections. The Secondary Criteria collected significant data in the following categories that are described below (see Appendix 6: for details):

- Clinical trial protocol and donor enrollment. Ranking value was increased by more consistent tissue donor clinical status, such as entry criteria (e.g. pathological stages), treatment regimen, standardized data collection and QC audits, and follow up. This category also placed value on accrual rates and the future ability to correlate molecular profile data with donor clinical data during the lifetime of the TCGA .
- Informed consent. These criteria were designed to ensure the broadest ability to protect patient rights, especially privacy, in TCGA since this project requires re-contacting

donors and will generate individual genomic information on a larger scale than previously seen in most research projects.

- MTAs. Collections were ranked on the basis of the institution's contractual capabilities and experience with distributing biospecimens for precompetitive data generation.
- Clinical data. Several criteria were used to assess the quality of clinical data, especially its accessibility (e.g., degree of electronic conversion required), degree of standardization, and its level of detail. Additional criteria evaluated the data in terms of compliance with patient confidentiality regulations (e.g., the Health Insurance Portability and Accountability Act of 1996).
- Sample characteristics. Significant ranking value was dependent on biospecimen quality, especially if the collection resulted from a relatively narrow range of donor diagnoses and sample histopathologies (e.g., stage, grade, and histological type), lack of precollection treatments that would alter molecular profiles, consistency and documentation of processing protocols, and consistency of biorepository management.
- QC. Biospecimen collections received additional value if the custodian biorepository had adopted formal protocols that include QC analyses of both tissue and molecular extracts.

The OCG staff applied the Secondary Criteria to candidate biospecimen collections on the basis of RFI responses, follow up questions and teleconferences with custodians, and site visits. In order of descending Secondary Criteria scores, the quantitatively ranked biospecimen sources were presented to the ETP for review and comment.

## **Final Selection**

The Final Selection process initiates the transfer of biospecimens from a source biorepository to the BCR. The process is ongoing as necessary for TCGA needs and is able to choose from among any of the biospecimen collections that passed the Primary Criteria, with preference being given to collections based on their ranking achieved during the Secondary Criteria evaluation stage.

### ***Final Selection Goals***

The goal of the Final Selection process was to include factors for consideration that were outside the control of the biospecimen source, yet were relevant due to timing, logistical, resource, TCGA scientific, and/or clinical reasons. Additionally, this final stage in the process provided an opportunity for an additional group of domain experts from the cancer research community and patient advocates, the ETP to consider the results of the Secondary Criteria step in conjunction with the Final Selection process.

The Final Selection process for TCGA biospecimens included consideration of several less quantifiable characteristics that were not a function of the biospecimen source and sample quality, including:

- Technical considerations, such as the timing of sample availability from the source and receipt by the BCR and potential unforeseen costs of transfer
- Scientific considerations relating to the types of studies (especially analytical technologies) of greatest interest to TCGA
- Health care burden considerations

- Clinical considerations, such as early research suggesting that genome characterization data from certain cancers are more likely to yield potential medical impact from the data generated during the TCGA pilot project

Candidate biospecimen collections were reviewed by the individual ETP members. Their analyses were provided to the NCI management group. They will evaluate all data obtained from the three-step process and will make a selection based on the aggregate information.

## Biospecimen Source Selection Process

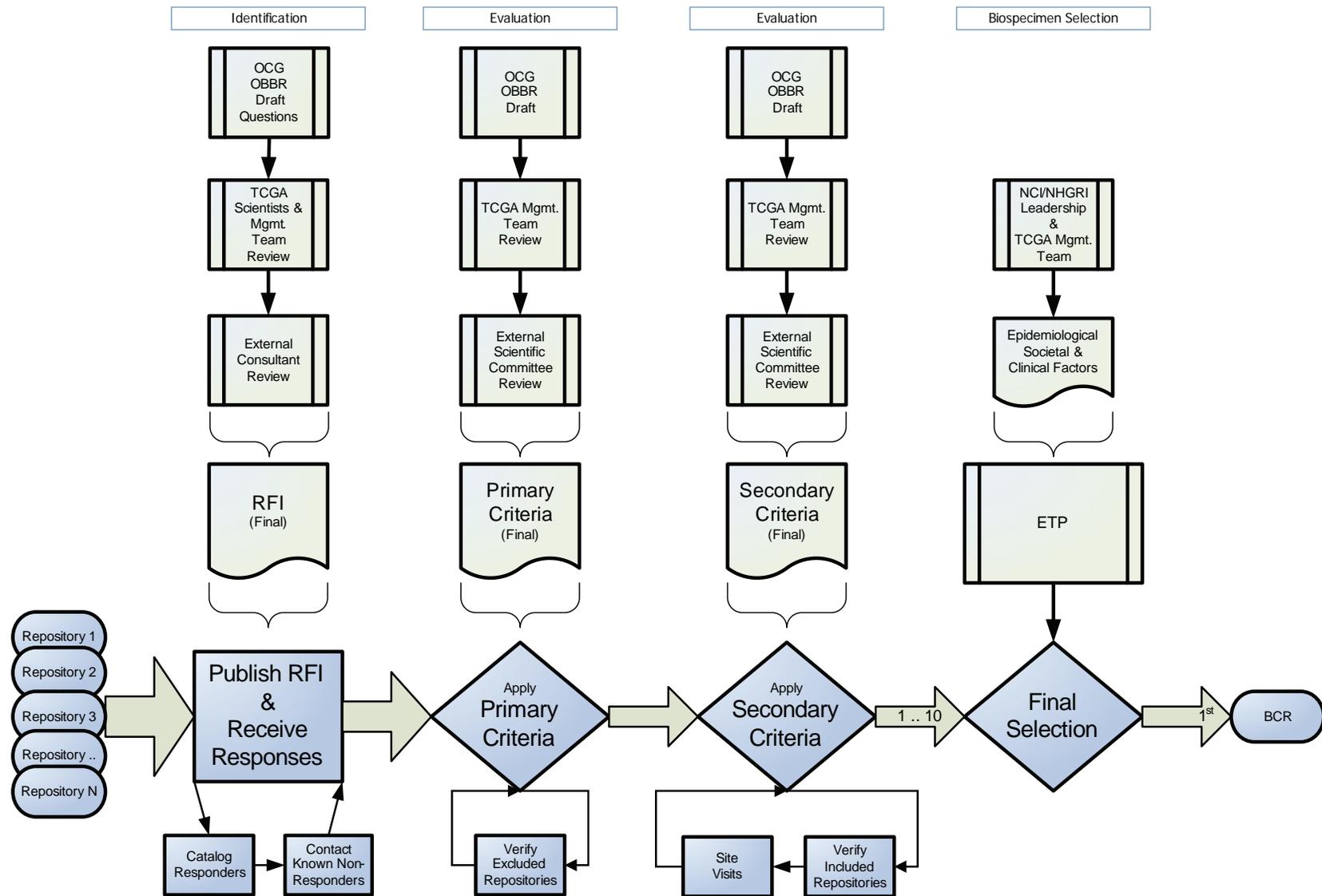


Figure 1. Process map of source biospecimen selection criteria development and evaluation. Horizontally are listed the identification and three evaluation stages in which the potential set of source collections was identified and then narrowed. Vertically are listed the steps undertaken to develop the RFI questions and selection criteria for each evaluation stage.

## **Appendix 1. Development of Biospecimen Selection Criteria**

The biospecimen selection process was based on a process to identify as many collections as possible via a broadly published RFI and then to narrow the candidates through three successive evaluation stages. The development of the RFI questions and all three selection criteria followed the general process outlined below:

- Establish the goal(s) for that stage of the process
- Gather draft questions or criteria from the TMT
- Review and iteratively modify criteria based on input from a broad set of internal staff members, TCGA advisers, and expert consultants
- Finalize the questions and selection criteria

At each evaluation stage, the candidate set of biospecimen collections was evaluated against the selection criteria as developed above:

- The evaluation stage was undertaken by the OCG staff, with review of the results by the staff of the Office of Biorepositories and Biospecimen Research (OBBR).
- Iterative review steps, including contacts with candidate biospecimen custodians for clarification and verification, were carried out by the OCG and OBBR staffs.
- Results of the evaluation process at each stage were documented and stored by the OCG.

### **Staff Members, Scientific Committees and Consultants**

A list of individuals and groups and their roles in providing input and critical review of questions and selection criteria is in Appendix 2.

#### ***TCGA Management Team (TMT)***

This group consists of internal staff members from the NCI and the NHGRI. The positions represented include program managers with responsibilities in cancer research; genomics; ethical, legal, and social issues; technology transfer and intellectual property (IP), and informatics.

#### ***TCGA External Scientific Committee (ESC)***

The ESC is responsible for reviewing and evaluating the progress of the members of the TCGA Pilot Project Research Network toward meeting their individual and collective goals. The ESC will provide recommendations to the Director of the NCI and the Director of the NHGRI about continued support of the components of the TCGA Pilot Project Research Network. The ESC is composed of senior scientists and clinicians with relevant expertise in cancer, genomics, and ethics; the members of the ESC are not principal investigators of a cooperative agreement involved in the TCGA Pilot Project.

#### ***Expert Consultants***

A large number of additional consultants, who provided critical review of the selection criteria and process, came from various NIH intramural divisions, clinical and nonclinical academic centers, NCI Cancer Centers, and for-profit and nonprofit biorepositories. The group included experts in the following fields:

- Ethical, legal, and policy issues, to ensure that biorepositories meet current regulations and societal standards for human subjects research protections, especially as they relate to the publication of genomic information.
- Technology transfer expertise in developing complex biological MTAs and associated IP structures, including the transfer of clinical data associated with biospecimens that are not anonymized.
- Patient and research advocates, who provided views on patient protection concerns, especially as related to TCGA's large-scale genomic data set creation.
- Molecular biology, for insight on the types of genomic analyses that will be performed initially and to identify novel technologies of the future. The development of new analytical technologies with different analyte extraction requirements will impact biospecimen procurement and preservation protocols.
- Genetics and statistics, to guide the requirements of sample purity needed for the current technologies as well as sample numbers to ensure the statistical power of the results.
- Pathology, to provide input on tissue selection criteria, collection and handling protocols, and histological QC processes.
- Bioinformatics, to evaluate criteria related to donor protection, biospecimen logistics LIMS support, clinical annotation, histologic and molecular QC data collection and management, data access and transfer, and caBIG compliance.
- Clinical practice and investigation, to provide a practical perspective on tumor tissue availability and characteristics from the perspectives of the operating room theater and pathology suite to ensure that TCGA analysis expectations can be met by the types, sizes, and numbers of tissue samples that can realistically be obtained by biopsy and resection.
- Cancer research, to provide guidance on disease selection, research needs for sample processing, and the key analytical technologies that will likely be applied to the biospecimens.

## **Request for Information**

The RFI was developed and published to elicit responses from all interested biorepository managers who might have biospecimens that meet the criteria for TCGA.

### ***RFI Development Process***

The draft RFI questions were developed by the OCG with input from cancer biologists, molecular biologists, pathologists, and clinical researchers who participated in early TCGA planning conferences. The draft questions were reviewed and modified during an "internal retreat" involving staff members from the NCI's Office of Technology and Industrial Relations, the OCG, the OBBR, and the Division of Extramural Affairs and the NHGRI's Division of Extramural Research, Ethical, Legal and Social Implications (ELSI) Research Program. The draft RFI was further reviewed by external consultants representing broad expertise in modern biospecimen collection. The final RFI was approved by the TMT.

### ***RFI Publication***

The RFI was issued on November 9, 2005, and was widely distributed. It was published in the *NIH Guide for Grants and Contracts* and on the Cancer Genome Anatomy Project and OCG websites and was publicized in numerous locations. The RFI was carried and referenced in

several publications, including the *Cancer Bulletin*, and a paid placement was made in *CAP TODAY*, a print and online periodical of the College of American Pathologists. Additionally, the RFI was sent to every NCI-designated Comprehensive Cancer Center and to over 350 participants of several biorepository symposia and TCGA project development conferences held during 2004 and 2005. See Appendix 4 for a list of publicizing outlets and meetings. The custodians of several nonresponding, but known, biorepositories were proactively contacted as well. Initially, RFI responses were due by January 12, 2006, but the date was extended, and responses were collected through March 17, 2006.

## **Primary Criteria**

The set of biorepositories identified by the RFI was next evaluated against the Primary Criteria, which are all binary (i.e., “yes” or “no” questions), and ALL must be answered positively for the candidate biospecimen collection to be further considered. If an answer from the RFI was missing or unclear, the OCG and the OBBR contacted the respondent for additional information.

### ***Primary Criteria Development Process***

The Primary Criteria were drafted by the OCG and OBBR staffs, after discussions and exploratory input from attendees at biospecimen and TCGA development conferences at which numerous biorepository managers were present. The draft primary criteria were then reviewed and modified by the TMT. These second-version draft Primary Criteria were then reviewed by the TCGA ESC before finalization.

### ***Primary Criteria Application***

The OCG and OBBR staffs performed the review of RFI responses against the Primary Criteria and contacted respondents when clarifying information was necessary. Biospecimen sources that did not pass the Primary Criteria were double-checked to verify validity of the exclusion. The review was performed using a worksheet similar to that in Appendix 5, with the results documented and stored in the OCG.

Those biorepositories that passed the Primary Criteria were then forwarded to the Secondary Criteria evaluation stage. Biospecimen collections that did not meet the Primary Criteria were further considered for the initial phase of TCGA pilot project.

## **Secondary Criteria**

For those candidate biospecimen collections that pass Primary Criteria evaluation, the Secondary Criteria will provide a ranking to further characterize the collections and assist in choosing only two or three cancer types that will be used during TCGA pilot project.

### ***Secondary Criteria Development Process***

The Secondary Criteria were drafted by the OCG and OBBR staffs, after discussions and exploratory input from attendees at biospecimen and TCGA development conferences at which numerous biorepository managers were present. These meetings included working groups that were tasked with developing specific recommendations for biospecimen collection as part of a general NCI-supported effort to develop “best practices.” The collective output from such working groups provided key input to the Secondary Criteria for TCGA biospecimens. The draft

Secondary Criteria were then reviewed and modified by the TMT. These second-version draft Secondary Criteria were then reviewed by Biology Subcommittee of the TCGA ESC.

### ***Secondary Criteria Application***

The evaluation of candidate biospecimen sources against the Secondary Criteria was performed by the OCG and OBBR staffs. In almost every case, the data collected on a source as part of the RFI process were insufficient to complete the secondary evaluation, and these biorepositories were recontacted to complete the data set so that the Secondary Criteria evaluation was as complete as possible. In each case, the actual scoring was performed by one staff member and validated by a second using the same scoring matrix. Furthermore, the initial four or five top-scoring biospecimen sources were site-visited by NCI and NHGRI staff members to check that the Secondary Criteria evaluation process was based on accurate data and to verify that source's inclusion. Documentation of input data sets and the scoring results are maintained by the OCG.

### **Final Selection**

The Final Selection process concludes with a decision to transfer a specific biospecimen collection from a source biorepository to the BCR. The process includes expert opinions from individuals representing the scientific, patient, and ethical communities based on the ranking results of the Secondary Criteria and a set of Final Selection criteria.

### ***Final Selection Criteria Development Process***

The Final Selection criteria were developed by the NCI leadership, the OCG, and the OBBR after input from the TMT. The criteria were influenced by discussions with a broad constituency including clinicians, cancer researchers, and advocates. The criteria were also based on input from the TCGA program staff with a view to logistical and timing issues.

### ***Biospecimen Expert Technical Panel***

The Biospecimen Expert Technical Panel (ETP) is a group of scientists, clinicians, patient advocates, and ethicists that met to provide input on the biospecimen collection evaluation data generated from the Primary and Secondary Criteria evaluations in concert with the nonbiospecimen considerations described above. The Panel's composition was not finalized until the deadline for the Cancer Genome Characterization Centers (CGCCs) submission passed to minimize the potential for conflicts of interest. In addition, ETP members recused themselves from analysis of any biospecimen source from their home institution if that institution submitted an application for the BCR contract or a CGCC grant.

It should be noted that, although not a component of this biospecimen source selection process, the BCR statement of work includes a second validation of the technical quality of biospecimens being imported to the BCR. If, for some reason, the biospecimens do not meet QC specifications, the BCR project managers will return to the prioritized list of tissues and select the next source.

## Appendix 2. Committees and Staff

### The Cancer Genome Atlas Pilot Project Management Team

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**Jane Peterson, Ph.D.**

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**Joseph Vockley, Ph.D.**

Senior Project Manager  
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**Mark Chee, Ph.D.**

Prognosys Biosciences, Inc.

**Geoff Duyk, M.D., Ph.D.**

Partner  
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**Ronald A. DePinho, M.D.**

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**Sean Eddy, Ph.D.**

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Fred Hutchinson Cancer Research Center

**Leroy Hood, M.D., Ph.D.**

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**Robert H. Waterston, M.D., Ph.D.**

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Department of Genome Sciences  
University of Washington

## Appendix 3. Request for Information

Notice of Information on Human Cancer Biospecimen Collections: Request for Information

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Notice Number: NOT-CA-06-002

### Key Dates

Release Date: November 9, 2005

### Issued by

National Cancer Institute (NCI), (<http://www.nci.nih.gov>)

NIH is seeking input from the community. This Request for Information (RFI) is for analysis and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the Government. The Government does not intend to award a cooperative agreement, contract, or grant on the basis of responses to this RFI or otherwise pay for the preparation of any information submitted or for the Government's use of such information.

### Background:

Cancer, with some exceptions, is a complex genetic disease in which mutations may contribute to its initiation and progression. Research has already identified a large number of mutations implicated in carcinogenesis, which has led to an understanding of many details underlying tumor development and progression. The successes of some newly introduced cancer drugs that act on known mutated proteins demonstrate that products of somatic genetic alterations are legitimate targets for therapy. However, given cancer's complexity, it is generally assumed that only a fraction of the molecular targets involved in carcinogenesis have been identified to date. The complexity of cancer is perhaps best exemplified by the fact that there are many different human tumor types, each with distinct subgroups, and each presenting radically different scientific and clinical challenges. This heterogeneity arises, in part, from the fact that cancer genomes are dynamic and tumors are complex systems that are shaped by chromosome aberrations, nucleotide mutations, epigenetic phenomena, the cellular and biological context of the specific cancer, characteristics specific to the individual patient, and environmental influences. While certain similarities exist across cancer types, any effort to characterize the genomes of cancers in a comprehensive, systematic manner must address important questions related to heterogeneity.

In February 2005, the Directors of the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) agreed to explore pursuing a 3-year pilot project, based on a recommendation in a recent National Cancer Advisory Board Biomedical Technology Subgroup Report (available at [www.cancer.gov](http://www.cancer.gov)), to determine the feasibility of cataloging the genetic aberrations associated with a set of human cancers. Since cancer is a genetic disorder, in principle it should be possible to derive a complete catalog of mutations, and in some cases to determine other abnormalities. Once the information is known, a complete understanding of the functional consequences of these alterations can be used to develop and implement preventative or interventional strategies to eliminate and/or control cancer.

**Information requested:**

A comprehensive definition of molecular taxonomy for cancer is an ambitious endeavor. One of the important initial challenges is to identify which cancer(s) to study in the pilot project that will optimize the chance for initial success. Any investigator with biospecimen collections within the United States, or internationally, is encouraged to respond to the RFI and provide the information requested below. Please note that it would be very desirable if respondents provide a separate response for each significantly different cancer biorepository that they maintain.

With regard to any clinical **protocols** that were/are used, respondents should indicate whether or not the collection of biospecimens was or is being carried out in the context of a clinical trial. If clinical trials were or are involved, please indicate whether or not:

- a single specific disease stage was or is one of the selection criteria;
- surgical treatments in each arm of the trial were/are identical;
- the samples and data were or are collected as part of a “linked” or “coded” protocol (meaning that the patients can be anonymously tracked for the purpose of attaching longitudinal and outcomes data to the samples in accordance with adherence to Federal patient privacy regulations and protections);
- the length of follow-up was or is greater than 5 years; and
- the current status of the protocol (active or inactive).

Further, with regard to any clinical **protocols** that might have been or are still being followed, respondents should, if possible, indicate whether or not:

- the patients were or are consented broadly or narrowly (i.e., specifically) for certain genetic analyses of the cancer and control samples;
- DNA sequencing was or is specifically permitted;
- the patients can be re-contacted for additional consent; and
- re-contact for additional consent from patients was or is specifically permitted in the original consent or it was/is accomplished via an institutional review board (IRB) waiver.

With regard to any **annotation** of biospecimens, respondents should, if possible, indicate whether or not:

- the biospecimen annotation included or includes demographic, clinical, and pathologic data;
- the data existed or exists in electronic format; and
- “electronic” data included or includes images of paper records.

With regard to the **contents of each biorepository**, respondents should provide, if possible, the following details:

- numbers of patients (unique cases) included in the collection;
- anatomic sites and histopathologic types (WHO classification) represented in the collection (e.g., lung and squamous cell carcinoma, respectively);
- numbers of tumors by grade found within each histologic type; and

- proportions of the specimens that represented or represent metastatic disease (and numbers of positive lymph nodes associated with each case, if available).

Further, with regard to the **contents of each biorepository**, respondents should, if possible, describe:

- the percentage of biospecimens that were or are > 200 mg in weight;
- the percentage of the biospecimens that were or are of unknown weight;
- the method of storage of the biospecimens that was or is used (e.g., fresh frozen, embedded in OCT, formalin-fixed and paraffin-embedded, and/or combinations thereof); and
- the existence and characteristics of any case-matched normal tissue biospecimens.

With regard to **standard operating, quality control, and quality assurance procedures**, respondents should, if possible, indicate whether or not:

- the time from cut-off of blood supply to stabilization (i.e., warm ischemia time) was or is collected as a data element for each specimen;
- the cellular composition of each sample was or is known;
- the fraction of biospecimens that were or are greater than 80 percent tumor;
- each biospecimen was or is subjected to the quality control processes, including:
  - individual pathology verification;
  - capture and storage of digital images;
  - molecular analyte testing (e.g., gel-based RNA degradation testing, 18S/28S rRNA ratios, etc.); and
- biospecimens in the collection would or could be available for the use in a Federally-supported Human Cancer Genome Project if determined to be suitable for its pilot phase of study.

The goal of this RFI is to identify and gather data about the characteristics of existing human tumor repositories. The information gathered from this process will help distinguish the key features of biospecimen collections that could meet the needs of the pilot cancer genome characterization project. The NCI welcomes any additional information the respondent wishes to submit, such as details of repository contents, collection procedures, biorepository management procedures, and human subjects protocols. Please attach such information as appendices to the main response.

### **Responses:**

The document should not be longer than five pages. It would be helpful if the data are provided in a tabular form. To assist you, we have provided two options for providing information directly through the CGAP web site ([cgap.nci.nih.gov](http://cgap.nci.nih.gov)). The response deadline is 8 weeks from the publication of this announcement; therefore, the closing date is January 12, 2006. If you choose to not fill out the form on the CGAP web site, please submit your responses to us either via mail or e-mail using the addresses shown below:

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## Appendix 4. RFI Publication and Distribution Channels

The RFI was published at these locations:

- *NIH Guide for Grants and Contracts* [website](#)
- NCI [Cancer Bulletin](#) for November 15, 2005
- *CAP Today*, December 2005 – periodical of the [College of American Pathologists](#)
- CGAP [website](#)

The RFI was sent to all NCI Cancer Center directors and administrators. This list can be found at:

- NCI-designated [Cancer Centers](#), the research-only Centers excepted

The RFI was sent directly to over 350 participants who attended the following conferences and symposia:

- “Exploring Cancer through Genomic Sequence Comparisons,” April 14-15, 2004 ([http://cgap.nci.nih.gov/Info/genomic\\_comparison](http://cgap.nci.nih.gov/Info/genomic_comparison))
- “Biorepository Coordinating Committee Workshop on Biospecimen Access and Ethical, Legal, and Policy Issues,” June 23-24, 2005
- “NCI Biospecimen Coordinating Committee Workshop: Best Practices and Recommendations for Establishing and Maintaining Biorepositories that Support Cancer Research,” July 18-20, 2005
- “Toward a Comprehensive Genomic Analysis of Cancer,” July 20-22, 2005 [http://cancergenome.nih.gov/about/TCGA\\_executive\\_summary.pdf](http://cancergenome.nih.gov/about/TCGA_executive_summary.pdf)

## Appendix 5. Primary Criteria

The following evaluation criteria were applied to the RFI responses. Each criterion is followed by a brief rationale for its inclusion.

1. Are there at least 250 individual tumor samples from unique adult cases, which, for all cases, include the following characteristics:

*This number was decided by the TCGA Management Team and the External Scientific Committee. The combination of two to three sample sets from each institution will provide a sufficient (statistically powerful) number of useful samples for most studies discussed during TCGA planning meetings.*

- Each tumor biospecimen weighs greater than 200 mg.

*200 mg of tissue, at least 80% tumor, should provide enough material for histopathologic QC and result in a sufficient quantity of biomolecules for the molecular analyses.*

- For every tumor biospecimen, a case-matched “normal” sample exists from which germline DNA can be obtained (e.g., 5-10 mL blood, uninvolved solid tissue). (If a lymphatic cancer, specify the source of “normal” DNA.)

*The molecular studies are to determine somatic changes, in which case a control sample is required.*

- If solid tissue, embedded in Optimal Cutting Temperature (OCT) solution.

*The research samples are physically distinct from the diagnostic biospecimen from which any sample-specific data would exist. Therefore, the research biospecimens must undergo histopathologic QC (i.e., sectioning, H&E stain, review) to verify disease, tissue, grade, and cellular composition. Embedding frozen, free samples is expensive and introduces a risk of altering the molecular profile during the warming that accompanies the embedding process.*

- The tumor samples represent a single histopathologic type, and if a solid tumor, do they represent a single cancer organ site (e.g., brain, breast, colon, etc.)?

*During the pilot, the goal is to study the purest samples (in terms of tissue of origin) possible to maximize the amount of comparable data that are generated.*

- Each tumor sample comprises at least 80% viable tumor cells (based on histopathologic examination of the actual research biospecimen OR of a physically adjacent region [e.g., the diagnostic biospecimen]).

*This cellular composition is realistically obtainable from certain tumor types and will maximize signal-to-noise ratios while eliminating the need for purification (e.g., LCM) and amplification (e.g., whole-genome amplification) processes during the pilot.*

2. Are all 250 samples in the collection described above obtained as part of a clinical trial or as part of a controlled molecular characterization study required as a prerequisite to entering a clinical trial?

*This is intended to ensure that donor samples are collected from a well-characterized cohort of donors with documented and standardized entry criteria, treatment, data collection, and followup.*

- If yes, is the trial or study closed, will it be closed by June 2007, or are the participants now (or by June 2007) unblinded?

*This criterion is intended to ensure that donor clinical information can be linked to the molecular profile generated from their tissues. If the tissue is collected within the context of a therapeutic trial, the participant's outcomes will likely be blinded until the study is complete.*

- If not, are the samples derived from a controlled observational study with uniform, standardized, and documented:

- Entry criteria

*This criterion is included to ensure uniform patient selection and minimize the variability of the donor's clinical situation, especially stage.*

- Treatment

*By minimizing the effect of surgical treatment variation on the tumor resection biospecimen, the molecular extraction protocols are more likely to generate uniform analytes.*

- Clinical data collection with standardized clinical reporting form (CRF) and regular QC audits

*TCGA requires high-quality, broad, and uniform clinical annotation of the biospecimens to support successful correlative studies.*

- Followup for capture of longitudinal information and outcomes

*Even though the samples going into the TCGA Pilot Project are treatment naive, it is expected that the study will eventually be able to support correlations among molecular profiles, treatments, and response. During the pilot, the controlled*

*variables that these two criteria ensure will help define the requirements for such studies.*

*In the context of a treatment validation trial, large numbers of patients are uniformly selected by prospectively determined entry criteria and uniformly treated according to a prospectively design protocol. All clinical data are collected in a uniform manner and long-term followup for each patient is typical. These features are highly unusual in any nontrial clinical (treatment) setting or in the context of an epidemiologic study. However, if these criteria are met in a specific milieu in which frozen biospecimen samples that meet the other TCGA criteria have been collected, the eligibility of the sample set would be recognized.*

3. Are the donors deceased?

If not, were the donors properly consented such that:

- The original consent permits reapproach for a secondary consent, or will the IRB grant a waiver to permit reapproach?
- The cohort can be contacted and reapproached from a practical/logistical perspective in order to obtain consent?

*The data generated from TCGA will include large databases of genetic and genomic information that, while deidentified, are extensive and individually unique. Furthermore, the data are not predesignated for use in a specific study. This level and purpose of data generation is unprecedented, and the project management consensus, informed by discussion with ethical, legal, and policy experts, is that this situation warrants a new informed consent process for each donor wherein the specifics of TCGA are laid out. If donors are deceased, the protocol is no longer considered human subjects research and the requirement for re consent no longer exists.*

4. Would the responder be interested in making the biospecimens available to TCGA?

(Institution)	Comment	Collection			
		Cancer 1 - Example		Cancer 2	
		Value	Comment	Value	Comment
Are there <b>at least 250</b> individual tumor samples from unique <b>adult</b> cases, and that for all cases include the following characteristics:			[This result is a derived value: "Yes" only if all 5 results below are also "Yes."]		
each tumor specimen weighs greater than 200mg.	Yes	75% > 200mg			
for every tumor specimen, a case matched "normal" sample exists from which germline DNA can be obtained (e.g. 5-10ml blood, uninvolved solid tissue)? (If a lymphatic cancer, specify the source of "normal" DNA)	Yes	Usually: adjacent solid tissue, sometimes blood.			
if solid tissue, embedded in OCT.	No	30% of samples are in OCT			
the tumor samples represent a single histopathologic type, and, if a solid tumor, primary cancer representing a single cancer organ-site (e.g. brain, breast, colon, etc.)?	No	All primary lung tumors, histopathologic types distributed as typical. Prof. X obtaining breakdown to check if 250 in one category.			
each tumor sample is comprised of at least 80% viable tumor cells (based upon histopathologic examination of the actual research specimen OR of a physically adjacent region – e.g. the diagnostic specimen)?	Yes	80% are >80%			
Are <b>all 250+</b> samples in the collection described above obtained as part of a clinical trial, or as part of a controlled molecular characterization study required as a prerequisite to entering a clinical trial?	No				
If yes, is the trial or study closed, will it be closed by June 2007, or are the participants now (or by June 2007) unblinded?	NA				
If not, are the samples derived from a controlled observational study with uniform, standardized and documented:		These collections are standard excess tissue from pathology review.			
Entry criteria	No				
Treatment(s)	Yes	Standard treatment regimen for this Dx at this medical center. All sample collected here.			
Clinical data collection with standardized CRF and regular QC audits.	No				
Follow-up for capture of longitudinal information and outcomes.	No				
Does the cohort include deceased donors?	Yes				
For those not deceased, were the donors properly consented and tracked such that:					
the original consent permits re-approach for a secondary consent, or will the IRB grant a waiver to permit re-approach?	No	Not in consent, IRB must be re-approached.			
the cohort be contacted and re-approached from a practical/logistical perspective in order to obtain consent?	Yes	75% of donors can be tracked.			
Would the responder be interested in making the biospecimens available to TCGA?	Yes				

## Appendix 6. Secondary Criteria

Secondary Criteria for Tumor Selection Ranking

Criterion	Description	Value	Sample Collection		Tumor Collection		Comments
			Answer	Points	Answer	Points	
<b>Protocol/Trial/Enrollment</b>							
If donors are/were in, or directed into, a therapeutic trial, how many drug treatment arms are in the trial?	Fewer is better in terms of sample biochemical variance.	1 arm = 5 points 2 arms = 3 points 3 arms = 1 point	1	5			
Do different arms of the trial have the same standardized and documented surgical treatment protocol?	Fewer is better in terms of sample format and tissue content variance.	Yes = 10 points	Yes	10			
If the protocol is closed, what was the date of closure?	Older protocols are more likely to have longitudinal and outcome data by now. (Enter protocol closed date.)	Every year = 2 points	1/1/2000	12			
If the protocol is still open:							
At what rate are donors continuing to be enrolled?	Creates option for more accrual	≥ 200/yr = 5 points 100 - 199/yr = 3 points ≤ 99/yr = 1 point					
Will the protocol be closed by June 2007 and, if applicable, be unblinded at the same time?	Unblinded (i.e. ability to correlate case vs. control to molecular profile) is required for correlative studies at pilot's close.	Yes = 5 points	Yes	5			
What fraction of the patients has NOT been lost to followup?	Better retention yields greater opportunity for correlating outcomes with molecular profile. Sliding scale to 0.	100% = 20 points	80%	16			
What is the mean length of followup (number of years)?		5 yrs - Lifelong = 5 points 3 - <5 yrs = 3 points					
Is/was a single specific clinical or pathologic stage one of the inclusion criteria?		Yes = 5 points	Yes	5			
Was/is absence of prior therapy for the current cancer a criterion for entry into this trial?		Yes = 10 points	Yes	10			

Criterion	Description	Value	Sample Collection		Tumor Collection		Comments
			Answer	Points	Answer	Points	
<b>Informed Consent/Permissible Use/Authorization</b>							
Does the source institution already have in place a process for patient recontact and recontact?		Yes = 10 points		0			
How many different IRBs will be required to approve the recontact process or sample/data transfer to TCGA?		1 = 5 points 2 or more = 0 points					
How many different merit review committees will be required to review and approve the sample/data transfer to TCGA?		1 = 5 points 2 or more = 0 points					
Did the institution specifically obtain a HIPAA-defined "authorization" for use of patient PHI in research?		Yes = 5 points	Yes	5			
Does the current informed consent permit DNA genotyping?		Yes = 2 points		0			
Does the current informed consent specifically permit DNA sequencing?		Yes = 2 points		0			
<b>Contractual Status/MTA</b>							
Has the donor institution already transferred samples from this biorepository to another third-party site?		Yes = 2 points		0			
Has the donor institution waived, or is it willing to waive, IP rights in data generated by TCGA from its samples?		Yes = 5 points		0			

Criterion	Description	Value	Sample Collection		Tumor Collection		Comments
			Answer	Points	Answer	Points	
<b>Clinical Data Quality</b>							
What is the frequency (in years) of data quality audits?		Yearly = 5 points Every 2 years = 3 points		0			
Does the annotation include standard demographic data: DOB, gender, race/ethnicity, occupation, and locale?		Yes = 1 point	Yes	1			
Does the trial CRF specifically attempt to collect annotation on any drug therapy prior to biospecimen collection?		Yes = 10 points		0			
Does the annotation include anatomic pathology reports on the tumor from which the research biospecimen was taken?		Yes = 5 point		0			
Is that annotation in CAP (College of American Pathologists) synoptic/checklist reporting format?		Yes = 2 points		0			
With digital images?		Yes = 2 points		0			
<b>Clinical Data Electronic Status/Standards</b>							
Do the data exist in electronic format (not including images of paper records)?		Yes = 10 points		0			
Are the data in a relational database system?		Yes = 10 points		0			
If so, is the data collection and management system validated as 21-CFR-11 compliant from a software technical perspective?		Yes = 10 points		0			
If not, are the data in an electronic grid/spreadsheet format?		Yes = 4 points		0			
Are the data characterized using caBIG Common Data Elements resident in caDSR?		Yes = 10 points		0			
Have the clinical data been specifically modified, or has the data access system been designed with specific functionality to prevent access to direct identifiers (such as name, SS#, MR#, phone number, etc.)?		Yes = 5 points	Yes	5			
Have the clinical data been specifically modified, or has the data access system been designed with specific functionality to permit export of clinical information compliant with HIPAA "de-identified" (i.e., non-PHI) or "limited data set" standards?		Yes = 5 points	Yes	5			

Criterion	Description	Value	Sample Collection		Tumor Collection		Comments
			Answer	Points	Answer	Points	
<b>Donor/Sample Characteristics</b>							
How many clinical stages do the enrolled donors represent?	Fewer is better.	1 stage = 10 points 2 stages = 3 points	1	10			
How many histopathologic grades do the tumor samples represent?	Sliding scale down to 0 points.	1 grade = 10 points	1	10			
What fraction of the tumors is primary versus a metastasis?	Sliding scale down to 0 points.	100% = 50 points	85%	43			
What fraction of the tumors comes from patients known not to have had a previous cancer?	Sliding scale down to 0 points.	100% = 10 points	85%	9			
If lack of prior therapy is NOT an enrollment criterion, what fraction of the tumor samples was acquired prior to disease-specific therapy (i.e., are the tumor samples chemo-, immuno-, hormonal, radiation, and alternative therapy naive)?	Sliding scale down to 0 points.	100% = 50 points	100%	50			
From the clinical surgical pathology report (i.e., not derived from review of the actual research biospecimen):							
If known, what fraction of the tumor samples contains less than 5% viable non-tumor cells?		100% = 5 points	85%	4			
If known, what fraction of the tumor samples contain <10% extracellular matrix?		100% = 5 points	85%	4			
What is the source of "normal" tissue case-matched with each tumor sample?		Blood = 10 points Adjacent tissue = 15 points Both = 30 points	Both	30			

Criterion	Description	Value	Sample Collection		Tumor Collection		Comments
			Answer	Points	Answer	Points	
<b>Sample Collection Protocol</b>							
Are <b>all</b> the biospecimens in this collection obtained and processed in the same institution at which the biorepository is housed?		Yes = 25 points					
			Yes	25			
If not, is <b>at least one</b> of the collection and processing protocols in the same institution at which the biorepository is housed?		Yes = 15 points					
			Yes	15			
Did the sample collection protocol begin with activities in the OR, or did it begin upon gross biospecimen receipt in pathology?		OR = 5 points					
Are the technical aspects of the surgical protocol (from which the tumor is obtained) standardized?		Yes = 10 points					
			Yes	10			
Were the samples collected, processed, and stabilized according to a single written SOP?		Yes = 10 points					
			Yes	10			
Have the laboratories and processes in which collection occurred been validated as GLP?		Yes = 15 points					
			Yes	15			
Are the following key sample collection process variables collected:							
In vivo clamp time?		Yes = 5 points	Yes	5			
Warm ex vivo ischemia time?		Yes = 5 points	Yes	5			
Collection to stabilization time?		Yes = 5 points	Yes	5			
Freezing/fixation time?		Yes = 5 points	Yes	5			
For hematologic cancers, is/was the "normal" blood sample collected posttreatment and tested for detectable cancer cells?		Yes = 10 points					
			Yes	10			

Criterion	Description	Value	Sample Collection		Tumor Collection		Comments
			Answer	Points	Answer	Points	
<b>Sample Storage</b>							
Have the OCT or blood or blood component samples been stored at -86 °C or liquid nitrogen?		IN <sub>2</sub> = 5 points -86 = 3 points					
Has the storage temperature been monitored and logged for life of sample storage?		Yes = 5 points	Yes	2			
Have the samples been accessed more than once since stabilization for any process that included warming? MORE-10		No = 5 points	Yes	0			
Are blood (component) samples stored as frozen whole blood, frozen separated PBLs, or frozen separated viable PBLs in DMSO (or equivalent)?		Whole blood = 0 points Separated = 5 points Viable PBL = 10 points					
Are all the samples labeled (or tagged) with a machine-readable unique identifier (e.g., barcode, RFID)?		Yes = 15 points					
<b>Research Sample QC</b>							
What fraction of the actual research samples has undergone pathology QC (i.e., sectioning, H&E stain, etc.)?	Sliding scale down to 0 points.	100% = 25 points	100%	25			
If performed:							
If known, what fraction of the research samples is greater than 80% viable tumor cells?		100% = 20 points	85%	17			
If known, what fraction of the research samples contains less than 5% viable nontumor cells?		100% = 5 points	85%	4			
If known, what fraction of the research samples contains <10% extracellular matrix?		100% = 5 points	85%	4			
Was a (semi-)quantitative value for necrotic composition captured?		Yes = 5 points	Yes	5			
Were representative digital images captured?		Yes = 5 points	Yes	5			
If >10% of the research samples have been extracted into RNA, for what fraction was the 18S/28S ratio determined to be greater than 1.5?	Sliding scale down to 0 points.	100% = 15 points	75%	11			