Agenda: To review and evaluate grant applications.

Place: Churchill Hotel, 1914 Connecticut Avenue, NW., Washington, DC 20009.

Contact Person: Mariela Shirley, PhD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 3186, MSC 7848, Bethesda, MD 20892, (301) 435–0913, *shirleym@csr.nih.gov.*

Name of Committee: Center for Scientific Review Special Emphasis Panel, Bioengineering, Technology, and Surgical Sciences Member Conflict.

Date: June 16, 2006.

Time: 2 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Roberto J. Matus, MD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 5108, MSC 7854, Bethesda, MD 20892, 301–435–2204, *matusr@csr.nih.gov.*

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine; 93.333, Clinical Research; 93.306, 93.333, 93.337, 93.393–93.396, 93.837–93.844, 93.846–93,878, 93.892, 93.893, National Institutes of Health, HHS)

Dated: April 20, 2006.

Anna Snouffer,

Acting Director, Office of Federal Advisory Committee Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

First-Generation Guidelines for NCI-Supported Biorepositories

AGENCY: National Institutes of Health (NIH), National Cancer Institute (NCI).

ACTION: Notice.

SUMMARY: The NCI is establishing common guidelines for the collection of biospecimens and their accompanying data by NCI-sponsored biorepositories. These guidelines are intended to standardize and enhance the quality of research material and data used in cancer research.

DATES: *Effective Date:* May 30, 2006.

ADDRESSES: These guidelines are open for public comment for a period of 30 days. After the comment period has closed, any comments received will be considered in a timely manner by the NCI Office of Biorepositories and Biospecimen Research and appropriate changes will be made and the final guidelines will be published and voluntarily in effect. After the effective date of publication of the final guidelines, written comments will continue to be accepted for the first year of implementation and can be sent to: First-Generation Guidelines, Office of Biorepositories and Biospecimen Research, Office of the Deputy Director for Advanced Technologies and Strategic Partnerships, National Cancer Institute, National Institutes of Health, 31 Center Drive, Room 10A03, Bethesda, MD 20892. Comments submitted via e-mail should use *biospecimens@mail.nih.gov* and enter ''First-Generation Guidelines Comment'' in the subject line. During the first year of implementation, the NCI will review any additional comments and experience with the guidelines to evaluate a possible need for future guidelines modification.

FOR FURTHER INFORMATION CONTACT: Implementation assistance and inquiries should be directed to senior staff of the relevant NCI Extramural and Intramural Program offices.

SUPPLEMENTARY INFORMATION:

I. Introduction

The guidelines assembled in this document are intended as a first step toward unifying policies and procedures for NCI-supported biorepositories. This process was initiated by the NCI through a multiyear process that began in 2002, including a 2004 report compiled for the National Cancer Advisory Board that showed substantial heterogeneity in biorepository management practices across the Institute (NCAB 2004). This study showed that NCI-supported biorepositories are not optimized in terms of operational, legal, and ethical policies and procedures, nor are they coordinated to provide a unique resource value. Specifically, it showed that:

- The NCI invests more than $50 million annually in biorepository programs, not including biorepositories supported through individual investigator grants, such as R01s.
- The 125 programs included in the study collected, maintained, and/or stored approximately 4 million human biospecimens in FY 2003.
- These programs support basic, epidemiologic, translational, and clinical research.
- Most programs collect frozen biospecimens and support genomic and proteomic research.
- Across the broad range of programs, there are no common standard operating procedures (SOPs) or Quality Assurance/Quality Control (QA/QC) measures.
- The programs lack a common database.
- There is no consistent, defined mechanism to access NCI-supported biospecimen resources.

II. Background

In 2005 the NCI took several actions to respond to these findings, including establishment of the Biorepository Coordinating Committee (BCC) in early 2005. The BCC is advisory to the NCI's Office of Biorepositories and Biospecimen Research (OBBR). The primary purpose of the BCC is to work with the OBBR to coordinate the NCI's biorepositories in a manner that optimizes the quality and accessibility of biospecimens for the broad cancer research community. Toward this goal, the OBBR and the BCC organized two workshops during the summer of 2005 to inform the development of specific recommendations on policy and operational issues. These workshops, which were based on the development of a series of white papers that consolidated documents and the overall knowledge base in biospecimens, brought together diverse representatives from the cancer research community as well as ethics, policy, and legal experts to discuss and propose approaches that could help unify, integrate, and improve the transparency of NCI-supported biorepository activities. The report and recommendations that resulted from the workshops are summarized in the document Harmonizing Processes and Policies for NCI-Supported Biorepositories, which was presented to the National Cancer Advisory Board in September, 2005. The report can be found at *http://biospecimens.cancer.gov/biorepositories/bcc_summary.asp.*

NCI defines a biorepository as a place, room, or container where human biospecimens are stored. Biorepositories may vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer.

Currently biorepositories serve as critical resources to the research community in the performance of postgenomics cancer research. It is becoming increasingly important that all biorepositories strive to achieve the best possible biospecimen quality, which would necessarily call for the adoption of consistent documentation, collection, processing, storage, and retrieval guidelines such as those outlined in this document. The workshops' recommended approaches were reported to the NCAB in September 2005. Proposed approaches, as well as additional meetings and work over the

past 3 years, form the basis of the first-generation NCI biorepository guidelines. These guidelines will be distributed to managers of all NCI-supported intramural and extramural biorepositories, who will be initially asked to conform to them on a voluntary basis. It is important to note that developing a workable set of guidelines is an evolving process that, with the emergence of new technologies and clinical practices, will require periodic revision. Therefore, these guidelines will be revised iteratively, with input from researchers, biorepository managers, advocates, policymakers, and related stakeholders.

III. Guidelines

Overview

1. Technical and Operational Guidelines

A. Biospecimen Collection, Processing, Storage, Retrieval, and Dissemination

1. Collect and process biospecimens under conditions appropriate for each biospecimen type and for the intended analyses, using collection protocols that are based on authoritative best practices or solid research data, when available. Ensure that proper informed consent protocols are followed.

2. Base all protocols on SOPs that are established using authoritative best practices or solid research data, when available.

3. Maintain a thorough and consistent level of biospecimen annotation while maintaining donor patient privacy pursuant to informed consent provisions.

4. Use a computerized inventory system that tracks the specific position of every stored aliquot. Each storage container should be labeled with a unique identifier. All other relevant information should be tied to this unique identifier. Inventory systems should contain security provisions sufficient to safeguard privacy and other informed consent provisions.

5. Develop a comprehensive quality management system (QMS). Standardized protocols should be applied consistently to ensure biospecimen quality and to avoid introducing variables into research studies. Document all collection and processing steps in the computerized inventory tracking system.

6. Ensure that all laboratory personnel are well qualified, trained to adhere to biorepository SOPs, and monitored for high-quality performance.

7. Ensure that a pathologist directs the collecting and processing of surgical and autopsy biospecimens to ensure that clinically important issues related to the biospecimens are adequately and accurately addressed and that patient care is not compromised.

8. Store biospecimens in a stabilized state. In selecting the biospecimen storage temperature, consider the biospecimen type, the anticipated length of storage, the biomolecules of interest, and whether goals include preserving viable cells. Use stabilizing agents as appropriate. Storage vessels should be durable under planned storage conditions. Follow consistent freezing and thawing protocols to ensure consistent quality for assays.

9. Establish rules for biospecimen disposal before storing the biospecimens in the biorepository and monitor compliance with the rules. Consider the anticipated storage interval when selecting storage conditions.

10. For tissue biospecimens, minimize the time for collection and processing as much as possible (unless inadequate processing time is known to interfere with the analysis method); reduce biospecimen temperature as soon as possible after collection. Optimal processing times may vary for other types of biospecimens depending on the analysis method for which they are used.

11. Establish inventory tracking systems and storage organizational methods to minimize disruption of the stable environment during sample retrieval.

12. Regularly review the performance of all long-term storage systems and equipment using standardized protocols.

13. Choose biospecimen containers with analytical goals in mind. This may require, for example, screening of containers for trace metals that may interfere with laboratory analyses.

14. Adhere to biosafety, packaging, and shipping regulations. Use a tracking system for biospecimen shipments. The biorepository should notify a recipient before shipping to confirm that the recipient can accept the package and properly store the biospecimen.

15. Retrieve biospecimens from storage according to SOPs that safeguard biospecimen quality.

16. When it is necessary to control biospecimen temperature during shipping, consider the shipping time, distance, climate, season, and method of transportation and modify distribution schedules accordingly, if possible. Ensure proper temperature during shipment, taking into account the type of biospecimen and its intended use. Tracking devices may be useful to ensure proper temperature throughout the shipment duration.

17. Prior to shipment, execute appropriate Material Transfer Agreements (MTAs) addressing donor privacy, as appropriate, intellectual property (IP), data sharing, and other similar requirements.

18. Consult International Society for Biological and Environmental Repositories (ISBER) best practices (ISBER 2005) for guidance on international transport regulations (governed by the International Air Transport Association) and information on classifying biospecimens for shipment. Train personnel in the shipment of biospecimens and update their training every 2 years. Maintain training records for all employees involved in shipping.

B. Collecting and Managing Clinical Data

1. Strive to collect and store all relevant clinical or epidemiologic data associated with a biospecimen, including, as study requirements dictate, longitudinal data. Follow applicable informed consent requirements and institute appropriate security/data-access control measures to address privacy issues. The NCI will work with biorepositories to establish a minimal ''universal'' clinical data set.

2. Use an informatics system that tracks all aspects of biospecimen collection, processing, and distribution to prevent biospecimen identification discrepancies and to support annotation.

3. Comply with applicable privacy and human subjects protection regulations governing the acquisition of biospecimens and associated clinical data. Link biospecimens to clinical data in compliance, as applicable, with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and U.S. Department of Health and Human Services (HHS) and U.S. Food and Drug Administration (FDA) human subjects protection regulations.

C. Quality Assurance/Quality Control (QA/QC)

1. Adhere to a written QMS. The QMS should describe the biorepository's QA/QC programs and approaches for ensuring that program requirements are met.

2. Require that staff be trained in QA/QC and maintain training records.

3. The SOPs should be printed in a manual that is readily available to all laboratory personnel and dated according to the most recent revision. The SOPs should state policies and define and describe procedures in detail. Develop procedures for

periodically reviewing and revising SOPs as necessary.

4. Establish security systems, including equipment monitoring and alarm systems that are monitored both locally and remotely, with plans to respond at any time. Emergency power systems should be ready to operate all critical equipment during power outages.

5. Use a data management system that includes a computerized inventory tracking system with appropriate security/access-control safeguards.

6. Develop a facility disaster plan based on a local area risk assessment. The plan should include appropriate measures to protect personnel and equipment during a disaster.

7. Maintain and repair all equipment according to SOPs. Establish preventive maintenance schedules.

D. Biosafety

1. Assume that all human biospecimens are potentially infective and biohazardous. Use universal precautions practices in biorepositories similar to those used in other laboratories and clinical settings. Handle biospecimens according to, at a minimum, Biosafety Level 2 (BSL–2) as outlined in the CDC/NIH booklet *Biosafety in Microbiological and Biomedical Laboratories.*

2. Immunize employees (*e.g.*, for hepatitis) when appropriate vaccines are available.

3. Develop a safety program and associated training procedures by identifying governmental and accrediting agency requirements regarding biohazards and likely sources of current information concerning laboratory biosafety. Among the agencies that oversee laboratory biosafety programs are the Occupational Safety and Health Administration (OSHA), the CDC, and the Clinical and Laboratory Standards Institute (CLSI).

4. Identify and address risks and other general issues of biosafety. Identify frequent biorepository activities and analyze safety issues involved with each activity. Take appropriate actions to ameliorate hazards.

5. Document all incidents where personnel are exposed. Response and treatment protocols should be prepared to be available in the event of potential exposure and infection.

6. Establish indemnification agreements with users of biospecimens except where prohibited by law.

7. Follow U.S. regulations concerning chemical safety, which protect employees from exposure to biohazardous levels of chemicals. Biorepositories should also develop a chemical hygiene plan in compliance with the OSHA's laboratory standards.

8. Properly ground freezers and other electrical equipment.

9. Establish fire emergency plans and practice them regularly.

10. Take precautions to prevent repetitive strain and back injuries and other accidents and injuries typical of the laboratory/biorepository environment.

11. For any laboratory or biorepository that processes radioactive materials, ensure that proper training of personnel and acquisition of necessary equipment to obtain licenses from the Nuclear Regulatory Commission (NRC) and/or local agencies are carried out.

E. Biorepository Informatics: Data Management and Inventory Control and Tracking

1. Assign a unique identifier (such as a number or barcode) to each biospecimen at the time of collection. Identify specific clinical and epidemiological data by the same number and/or barcode. Use the number or code to track a biospecimen from collection through processing, storage, and distribution.

2. Update the biorepository database each time a biospecimen is moved within or out of the biorepository.

3. Use informatics systems that support the linking of biospecimens with associated research data and, when available, the limits, if any, on the use of the sample. When applicable, track the levels of consent that each patient has given for the use of their biospecimens and whether that consent has been withdrawn.

4. To protect the health information of patients, adhere to privacy laws with respect to informatics systems.

5. The NCI Center for Bioinformatics (NCICB) has developed additional bioinformatics guidelines and tools that address the issues of functionality of informatics systems, integration with existing systems, and interoperability among individual systems at biorepositories. The NCICB has developed the **Ca**ncer **B**iomedical **I**nformatics **G**rid, or *caBIG*™. caBIG (see *https://cabig.nci.nih.gov/*) (NCI 2005) is a voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools. caBIG silver-level compatibility is recommended for NCI-supported biorepositories (see *https://cabig.nci.nih.gov/guidelines_documentation*).

2. Ethical, Legal, and Policy Guidelines

A. Informed Consent

1. Use a process of informed consent for each biospecimen collection event. The NCI will provide all of its biorepositories with a sample consent template, which should be reviewed and adapted by the relevant IRB. Biorepositories should adapt the template to their needs. The consent form should address the use of biospecimens or data by private entities, the possible future development of commercial products through research, and the release of individual research results to participants.

2. Allow research participants to specify the types of research for which their biospecimens may be used, including use in additional future projects.

3. Document clear policies for biospecimen and data access.

4. Develop policies to handle biospecimens and data for which consent has been withdrawn.

5. Monitor the need for obtaining informed consent when the biorepository houses identifiable biospecimens and data from children, that were obtained with parental or guardian permission, when a child reaches the legal age to consent for a research study.

6. Consider FDA regulations concerning research on existing biospecimen collections, for any study that could involve FDA oversight in the future. These regulations do not exempt in vitro studies from the requirement for documented, institutional review board (IRB)-approved consent from the sources, even in cases where biospecimens have been deidentified.

7. Establish and document transparent policies governing the retention of records and biospecimens. For clinical biospecimens, State laws may also govern how long records must be retained. For research specimens, the ideal is permanent storage if resources and storage space are sufficient. However it should be noted that biospecimens degrade over time and/or may no longer be useful due to changes in science and technology.

For additional information about IRBs and the requirement for the HHS Office for Human Research Protections (OHRP)-approved assurance of compliance, see the OHRP Web site at *http://www.hhs.gov/ohrp/*. Specific OHRP guidance concerning tissues and biorepositories is included among the documents referenced at *http://www.hhs.gov/ohrp/policy/index.html#tissue.*

B. Access to Biospecimens and Data

1. Establish clear guidelines for sample distribution (and clinical data sharing) consistent with ethical principles, prevailing laws, and, if applicable, consent form language. The guidelines should be flexible so that biorepositories may respond to changing scientific needs.

2. Ensure that investigators have timely, equitable, and appropriate access to human biospecimens and associated clinical data stored at NCI-supported biorepositories without undue administrative burden. Access should be guided by policies and procedures such as the following:

- Scientific validity of the research proposal.
- Investigator's agreement covering confidentiality, use, disposition, and security of biospecimens and associated data.
- Investigator's written agreement in a Material Transfer Agreement to comply with the NIH Research Tool Guidelines. (*http://ott.od.nih.gov/policy/rt_guide_final.html*).
- Investigator and institutional research qualifications.
- Ethical oversight where required by Federal regulations or local institutional requirements.
- Adequate funding for the biorepository.

In addition to the above, the following points should also be considered while assessing access privileges:

a. Biospecimens and associated clinical data should be appropriately matched with the specific scientific investigations for which they are intended.

b. The local decision-making body should take local principles into account. Ethical considerations should come first among principles that guide the decisionmaking process.

c. Biorepositories should establish an appeals process for addressing disputes over allocation decisions.

3. Apply guidelines to all new collections and, whenever possible, to existing collections.

4. If applicable and where monetary charges are necessary, charge only to recover costs as appropriate to retrieve and disseminate specimens.

5. If a biorepository must close due to lack of funding or otherwise cannot maintain or use the biospecimens, the availability of biospecimens should be announced for transfer to the research community (*e.g.*, via a Web site). Transfer should be consistent with the informed consent and allowable use of biospecimens.

6. Within the biorepository, use a system of data access with defined levels of access privileges. Restrict access to research subjects' identities and medical, genetic, social, and personal histories to necessary biorepository staff members who need such access as part of their duty or to persons permitted access by law. Monitor personnel compliance with access restrictions.

7. Store human biospecimens only for research purposes according to approved protocols, not to serve individual research participants' needs or wishes.

C. Privacy Protection

1. Institute the level of security appropriate to the type of biorepository and to protect study participant privacy for the biospecimens stored in the biorepository.

2. In applications for support, include documentation of policies, mechanisms for auditing the effectiveness and enforcement of policies, required training, and security measures pertaining to employee access to data or biospecimens.

3. Institute the level of security appropriate to the type of biorepository.

D. Custodianship

1. In the application for proposal for biorepository funding, propose plans for formal and continuing responsibility for custodianship (not ownership) of collected biospecimens and associated data as part of the biorepository protocol.

2. In the application for proposal for biorepository funding, also address plans for the handling and disposition of biospecimens and associated data at one or more of the following points: (a) End of the active support of the grant, (b) accomplishment of the specific research objectives of the study, (c) depletion of biospecimens, and/or (d) achievement of critical data endpoints.

3. Require disclosure of financial or professional conflicts of interests of biorepository personnel, consistent with institutional procedures and policies.

4. Use clear and specific informed consent language to ensure that those who contribute biospecimens and/or data for research purposes are fully informed that the research done with these biospecimens may help develop products, tests, or discoveries that may have commercial value (also see A.1. above).

E. Intellectual Property

1. For the transfer of materials in academic-industrial collaborations, use the NIH Simple Letter Agreement (SLA), the Uniform Biological Material Transfer Agreement (UBMTA), or other MTA with terms consistent with the NIH Research Tools Policy and NIH data sharing policies, *e.g.,* the Final NIH Statement on Sharing Research Data. These agreements should be modified where necessary to cover human subjects research. A sample NIH SLA modified to address the transfer of human biospecimens is attached as Appendix 2.

The following Internet sites are relevant to this issue:

- *http://ott.od.nih.gov/policy/research_tool.html.*
- *http://www.autm.net/aboutTT/aboutTT_umbta.cfm.*
- *http://grants1.nih.gov/grants/policy/data_sharing/index.htm.*

2. Recognize that biorepository staff members as custodians of biospecimens are not *a priori* considered inventors under patent law for inventions made using materials distributed by the biorepository. In general, the staff should be informed that one whose sole contribution to an invention consists of the routine collection, handling, storage, and disbursement of biospecimens might not rise to the level of ''inventor'' of an invention. Inventorship is determined by patent law and must be considered on a case-by-case basis by trained legal personnel.

3. Recognize that biorepositories have no inherent rights to future IP, including reach-through rights in inventions made by investigators using samples obtained from the biorepository.

4. Ensure through MTAs that research data developed using biospecimens are made available to the research community. (See sample in Appendix 2.)

Guidelines Details

1. Technical and Operational Guidelines

A. Biospecimen Collection, Processing, Storage, Retrieval, and Dissemination

Although the specific mission of a biorepository will result in the use of different collection and processing procedures, common principles should apply to all biospecimen types. The guidelines below are based on current, published information and will be revised periodically as new information is generated from ongoing research projects.

Determining Which Biospecimens To Collect

1. *Collection priorities should be based on the defined purpose of each NCI-supported biorepository in supporting specific types of research.* Biorepositories should track researchers' requests to guide the collection and

storage process and to attempt to anticipate which biospecimen types (*e.g.,* matched blood, serum, plasma, buffy coat, saliva, urine) will make the biorepository most useful for future research. Researchers should involve biorepository scientists as early as possible during study planning to develop a strong approach for biospecimen collection.

2. *NCI-sponsored biorepositories should strive to collect materials from diverse populations representative of the United States.* However, this goal may depend on the specific purpose, such as the disease focus, of the NCI studies supported by the biorepository.

Biospecimen Collection and Processing

Biospecimen collection occurs in many contexts, including surgical procedures, organ donation and transplantation, autopsies, venipuncture, and evacuation; for population-based studies, collection may occur in field locations such as hospitals or study participants' homes.

1. *The NCI will provide guidance in the future on guidelines for biospecimen collection while allowing for flexibility when new methodologies are warranted.* SOPs will enhance the comparability of research results and help make biospecimens interchangeable. This guidance will include:

- Collection protocols for various biospecimen types based on solid research data.
- A high level of biospecimen annotation, consistent across NCI-sponsored biorepositories, recording key data, such as time to banking, time of ischemia, time of biospecimen excision, character of chemical preservation, time of fixation, etc. For paraffin-embedded biospecimens, it may prove important for the interpretation of analytic data derived from these biospecimens to have documentation of the specific protocol through which a biospecimen was processed before it was placed in paraffin. Appropriate and complete documentation surrounding biospecimen collection, processing, and storage are essential and relevant to the quality of research data to be obtained.
- Uniform, nonredundant sample nomenclature across NCI-sponsored biorepositories.
- State-of-the-art sample tracking procedures and supporting informatics.
- A QMS to ensure adherence to standards.

2. *Biorepositories should record data relevant to research goals.* As appropriate for the study, for all types of biospecimens, the amount of time elapsed during collection and processing should be recorded and tracked in the biorepository informatics system. Biorepositories should also record data on the collection and processing procedures used.[1]

- For tissue biospecimens, the time for collection should be minimized as much as possible; biospecimen temperature should be reduced as soon as possible after collection. Biospecimen processing time should be minimized if freezing is the stabilization endpoint. If fixation is the stabilization endpoint, control of processing time between maximum and minimum durations may be required.
- Rapid processing may not be as critical for other types of biospecimens, such as blood, and optimal processing times may vary depending on the analysis method for which a biospecimen is used. Examples of data to record for blood biospecimens include collection time relative to treatment or other interventions, time of day at collection, whether the patient was fasting, and whether he or she was sitting or standing during collection.

3. *NCI-supported biorepositories should seek to use the processing method that preserves the greatest number of analytes, unless the aim of a particular study specifically requires alternative processing.* To select processing methods (such as freezing, fixation, and the use of stabilizing additives), a biorepository should define its goals and the research priorities of the studies it supports. Procedures should maximize the potential for biospecimen distribution and research use. When possible, individual biospecimens should be divided into aliquots or fractions and/or preserved by multiple processing methods. Biorepositories that validate biospecimen quality for specific research applications should use as little of the biospecimen as possible.

Biorepository Personnel

Personnel involved in biorepository management and use, including researchers, technicians, nurses, surgeons, pathologists, anesthesiologists, and assistants, should be aware of the purpose and goals of the biorepository. To ensure the collection of high-quality biospecimens for research, collection, and processing, personnel should be well qualified and trained to adhere to applicable SOPs. A pathologist should be involved for expertise in collecting and processing surgical and autopsy biospecimens. It is important that a pathologist determine what tissue is necessary for pathologic diagnosis and what is excess and can be given to the biorepository for research purposes. This is crucial in ensuring that patient care is not compromised.

Biospecimen Storage

The following general guidelines section applies to all types of biospecimens, such as wet tissue, frozen tissue, paraffin-embedded tissue, glass slides, blood, serum, and urine. Individual types of biospecimens should be handled according to SOPs specific to each biospecimen type and to the biomolecules to be analyzed in that biospecimen type (*e.g.*, RNA, DNA, protein, lipid, etc.).

1. *Standardized protocols should be applied consistently in preparing and storing biospecimens to ensure their quality and to avoid introducing variables into research studies.* Biorepositories should record storage conditions and especially deviations from SOPs, including information about temperature, thaw/refreeze episodes, and equipment failures. Each piece of storage equipment should have a log containing the manufacturer's manual, records of equipment operation, and descriptions of maintenance, repairs, and calibration. Storage conditions should be recorded automatically, and the performance of all long-term storage systems and equipment should be reviewed annually using standardized protocols (Mager *et al.* 2004). Calibrated devices should be used to validate automated temperature measurements.

2. *Biospecimens should be stored in a stabilized state.* For blood biospecimens, all components should be stored where possible. This is particularly important for large, population-based studies, for which it is difficult to predict how biospecimens will be analyzed in the future.

A biorepository should avoid unnecessary thawing and refreezing of frozen biospecimens or frozen samples of biomolecules extracted from the biospecimens. When thawing/refreezing is necessary, a biorepository should follow consistent and validated protocols to ensure continued stability of the analytes of interest. Methods, such as inventory tracking, should be established to minimize disruption of the stable environment during sample retrieval.

In selecting biospecimen storage temperature, consider the biospecimen type, the anticipated length of storage,

[1] *NCI will support research to determine the effects of various biospecimen processing methods on analyte preservation.* Biorepositories should continually attempt to improve collection and processing methods to maximize the quality of materials for molecular analysis. NCI-supported biorepositories should document the effects of different processing methods and develop guidelines for biospecimen processing based on the goal of preserving various analytes.

the biomolecules of interest, and whether goals include preserving viable cells. Paraffin blocks should be stored at temperatures below 80 °F (27 °C) in an area with pest and humidity control. In the case of *liquids*, such as blood and urine, consider separating biospecimen components before storage to preserve each constituent under its optimal condition. However, whole-blood (rather than fractional) cryopreservation is recommended as an efficient and cost-effective option for processing viable cells in large-scale studies (Hayes *et al.* 2002). When in doubt as to possible future uses, store *tissues* in the vapor phase of liquid nitrogen freezers to ensure long-term viability. Lower storage temperatures and the use of a cryoprotectant (such as DMSO) are recommended to maintain viable cells for long periods of time (ISBER 2005). Planned analyses should consider the difference in temperature between the bottom and top of a liquid nitrogen freezer; the temperature at the top of a liquid nitrogen should be consistently below −140 °C.

Avoid self-defrosting freezers that cause damaging effects to biospecimens, even those in capped tubes, by enhancing desiccation (Holland *et al.* 2003).

3. *Biorepositories should establish rules for disposing of biospecimens before storing them.* Consider the anticipated storage interval when selecting storage conditions. If possible with available resources, store control biospecimens under each condition used in the biorepository and assess these control biospecimens at regular intervals to assess the effects of storage time on desired qualities such as viability, preservation of morphology, and biochemical integrity.

4. *Storage vessels should be stable under planned storage conditions.* Vial size and number should be suitable for typical aliquots, anticipated investigator uses, and number of investigators. Volume and type of containers should prevent sample loss and minimize the costs of collection and storage. Screw-cap cryovials should be used for long-term, low-temperature storage; glass vials or vials with popup tops are unsuitable for long-term storage (Caporaso & Vaught 2002). Wrap snap-frozen biospecimens in aluminum foil or place them in commercial storage containers to minimize desiccation (Grizzle 2004). Choose labeling and printing systems that will be stable under the long-term storage conditions appropriate for the biospecimen. Face shields and appropriate gloves should be worn for worker protection.

Biospecimen containers should be chosen with analytical goals in mind. For example, when samples will be tested for the presence of xenobiotic chemicals, containers should be free of xenobiotic contamination. Certified RNase-free containers should be used for all steps in handling RNA samples.

5. *Each storage container should have a unique identifier for the biospecimen aliquot that is firmly affixed to the container, clearly and legibly marked, and able to endure storage conditions.* All other relevant information should be tied to this unique identifier, bearing in mind study participant confidentiality, security, and informed consent provisions. Inventory systems should relate the presence of each aliquot to its specific position in a specific freezer, refrigerator, or shelf.

6. *Automated security systems should continuously monitor the function of storage equipment.* Backup equipment, such as an alternative power source, should be automatically activated when necessary. Emergency procedures should be in place if freezers fail or exceed a preset temperature. SOPs should be in place for alerting personnel and for moving biospecimens to alternative storage locations. Biorepository SOPs should include procedures for responding to severe weather and floods as well as specific power and equipment failures. Personnel should be trained in safety related to biospecimen handling, use of equipment, and SOPs for responding to emergency situations. For particularly valuable biospecimens, an empty, functioning freezer should be available in case of single-freezer failure. Also consider storing replicate biospecimens in at least two different locations to safeguard against storage or handling failures (*NBN Blueprint 2003;* Landi and Caporaso 1997; Caporaso and Vaught 2002; Eiseman *et al.* 2003).

Shipping Biospecimens

1. *Retrieval.* Biospecimens should be retrieved from storage according to biorepository SOPs that safeguard biospecimen quality. Before retrieval, systems should be in place to verify that the request has received approval from the appropriate committee(s). SOPs should include a checklist to confirm completion of the retrieval process. Document deviations during retrieval, such as inventory inconsistencies, damaged containers, thawing or refreezing, etc.

2. *Shipping conditions.* When seeking to regulate biospecimen temperature during shipping, consider the shipping time, distance, climate, season, method of transportation, and regulations as well as the type of biospecimens and their intended use (Landi and Caporaso 1997). The number of biospecimens per package also affects whether temperature can be maintained for all biospecimens in the shipment. Send a prior test shipment, of frozen water samples for example, before shipping extremely valuable samples, to check the adequacy of coolants and any potential obstacles to a successful shipment. In addition, conditions throughout a critical shipment can be monitored by enclosing a device that records temperature during transport. Placing samples in sealed bags with a desiccant can be used to control humidity.

To maintain proper temperature during shipping, use appropriate insulation, gel packs, dry ice, or liquid nitrogen (dry shipper). To maintain refrigerated temperatures (2°C to 8°C), use gel packs conditioned at −15°C or phase change material rated for refrigerated transport. To maintain frozen temperatures, use gel packs conditioned at or below −20°C. For frozen temperatures at −70°C, use dry ice pellets or sheets. Note that dry ice is considered a hazardous substance for shipping purposes. For maintaining temperatures at or below −150°C, use a liquid nitrogen dry shipper (ISBER 2005). Use insulated packaging to protect biospecimens from extremely hot or cold ambient conditions. Whenever intending to maintain samples below ambient temperature, include enough refrigerant to allow for a 24-hour delay in transport (ISBER 2005). Temperature-sensitive material should be handled by a courier with resources to replenish the refrigerant in case of a shipping delay (ISBER 2005).

Paraffin blocks and slides should be shipped at room temperature in an insulated package via overnight carrier. The use of insulated packages is important to minimize the effect of temperature fluctuations and to protect the blocks from temperatures higher than 80°F (27°C). Flat biospecimens, such as dried blood samples on absorbent pads or cards, should be enclosed in watertight plastic bags and shipped in a sturdy outer package or commercial envelope. Samples on glass or plastic slides should be cushioned and shipped inside a sturdy (not flexible) outer package. Triple packaging should be used for liquid samples.

3. *Documentation.* The biorepository should notify a recipient before shipping to confirm that the recipient can accept the package and properly store the biospecimens. Packages should be bar-coded and tracked by the biorepository and the recipient. A

biorepository shipping log, either written or computerized, should track shipments from and to the biorepository and include the following information: shipment/invoice number; recipient (or source); date shipped (or received); courier name and package tracking number; sample description; number of samples shipped (or received); condition on arrival; study name and number, if available; key investigator's name; and signature of biospecimen recipient (ISBER 2005).

Standardized paperwork should accompany shipments. Biorepository personnel should send a shipping manifest, a list of sample identification numbers, and descriptions of samples electronically to the biospecimen recipient and include a hard copy of the manifest in the shipment itself. Identifying data should be available for the use of shipping or customs agents as well. Some shipping agents require an itemized list of contents between the secondary and outer packaging of diagnostic biospecimens.

Biorepository personnel should verify biospecimen labels and pathology reports against the packing list for consistency and correctness.

A feedback questionnaire should be enclosed in each shipment for QA/QC purposes, requesting feedback about the quality of samples received (Eiseman *et al.* 2003).

4. *Regulatory considerations.* Consult ISBER Best Practices (ISBER 2005) for information concerning international transport regulations and classifying biospecimens for shipment. Failure to conform to international air transport regulations will result in delay or refusal of shipment and probable biospecimen deterioration. Regulations must be followed precisely, since improperly packaged or labeled goods will be refused for transport by airlines or delayed at customs (Holland *et al.* 2003). For international shipments, biorepository personnel should prepare safety declarations for foreign customs (Landi and Caporaso 1997).

For packaged biospecimens, International Air Transport Association (IATA 2004) regulations require three packaging components: (1) A primary inner receptacle, (2) secondary packaging, and (3) rigid outer packaging. The primary receptacles should be packed in the secondary packaging so that, under normal conditions of transport, they cannot break, be punctured, or leak their contents into the secondary packaging. Secondary packaging should be secured in outer packaging with cushioning material. Secondary containers for diagnostic biospecimens should be certified by the manufacturer prior to use. Outer packaging is regulated as to material, size, and ability to withstand a 1.2-meter drop test as outlined in IATA Section 6.6.1. Leakage of the contents should not affect the cushioning material or outer packaging (IATA 2004). Some shipping agents designate the same three layers of packaging and absorbent material between outer and secondary packaging. Specifics of the primary containers for diagnostic biospecimens, liquid biospecimens, and solid biospecimens are described on the shipping agents' Web sites. Styrofoam® chests containing dry ice may be used to ship samples that should be maintained at low temperatures (Landi and Caporaso 1997). However, the shipping agent may exclude Styrofoam® as an acceptable outer packaging. To confirm that shipping conditions meet sample needs, shipping personnel should review test reports from packaging that has been tested to meet regulation requirements. Packaging should be used in the same configuration under which it was tested (ISBER 2005).

Consult OSHA regulations to determine whether a substance requires a biohazard label. Ship Category A infectious substances in accordance with IATA Packing Instruction (PI) 602 (IATA 2004). Ship Category B infectious substances (also designated as diagnostic specimen, clinical specimen, or biological specimen, category B) in compliance with IATA PI 650.

Ship dry, noninfectious biospecimens (*e.g.,* dried blood, tissue, saliva, or hair) with special packaging as specified by the shipping agent. Wet-fixed biospecimens shipped in formalin/formaldehyde should include ''ICAO/IATA'' under *additional handling information* (Grizzle 2004).

5. *Training.* Training of personnel for shipment of biospecimens is strongly recommended (ISBER 2005). Training should be updated at least every 2 years. Dangerous goods training may be required for some biorepository personnel. A record of training should be maintained of all employees involved in the shipping process. Training and certification are available through various shipping vendors (ISBER 2005). On completion of training, the training organization issues a certificate of completion.

B. Collecting and Managing Clinical Data

Extensive annotation of tissue biospecimens is crucial to the overall usefulness of the biorepository as a resource for scientific research (Eiseman *et al.* 2003). Biorepositories store biospecimens collected using multiple methodologies and procedures, including tissue collection, blood draws, and buccal cell and urine collections. Researchers rely on banked biospecimens for a wide variety of purposes, including target discovery and validation, prevention research, research on early detection, genetic studies, and epidemiologic analyses. The data recorded by biorepositories depend on the types of biospecimens they collect and the studies they support. It is critically important for excellence in research that NCI-supported biorepositories use SOPs for biospecimen collection, processing, and storage. While harmonization of these procedures is the ultimate goal, the NCI is engaged in research to identify the best set of protocols and methods to produce high-quality biospecimens. Regardless, biospecimens must maintain donor privacy in all collection of clinical data.

Determining Data Sets

1. The NCI will define *the minimal clinical data to be collected for all biospecimens, as appropriate for the research protocol* at NCI-supported biorepositories. This universal set will change over time. Biorepositories should adopt the harmonized nomenclature being developed by the NCI for clinical data and establish algorithms to translate raw data into standard nomenclature.

2. NCI-supported biorepositories should *establish additional data categories for specific types of research.*

Collecting Clinical Data

1. NCI-funded biorepositories should strive to *collect and store all relevant clinical data associated with a biospecimen.* This will maximize the use of biospecimens for current and future short-term and longitudinal studies. Biorepositories should encourage participating investigators to annotate biospecimens to the fullest extent possible consistent with biorepository goals and/or study design. Data collection activities should conform to FDA requirements if and where applicable, so that the data can be cited and/or used in Investigational New Drug and Investigational Device Exemption applications.

2. The NCI will develop *a tiered system of clinical data annotation,* which will define the potential of any given biospecimen in supporting high-quality research and will guide decisions on the appropriate use of biospecimens by the scientific community.

3. NCI-supported biorepositories should *employ a uniform, nonredundant vocabulary* (caBIG common data elements [CDEs]) for clinical data across sponsored biorepositories.

4. NCI-supported biorepositories should *track researchers' requests* for specific clinical data to guide refinements of data collection guidelines.

5. NCI-supported biorepositories should employ *a method for validating the clinical data collected*. These data should be validated to ensure accuracy in downstream scientific research.

6. NCI-supported biorepositories should comply with applicable privacy and human subjects protection regulations governing the acquisition of biospecimens and associated clinical data. Biospecimens should be linked to clinical data in compliance, as applicable, with the HIPAA regulations and with HHS and FDA human subjects protection regulations.

Longitudinal Clinical Data [2]

1. As the study requirements dictate, NCI-supported biorepositories should *collect and store longitudinal* data following applicable informed consent requirements.

2. Depending on the study design, information linked to samples should include demographic data, lifestyle factors, environmental and occupational exposures, cancer history, structured pathology data, any additional diagnostic studies, information on initial staging procedure, treatment data, and any other information relevant to tracking a patient's future status for clinical outcomes. NCI-supported biorepositories should facilitate followup with patients.

3. NCI-supported biorepositories should *maintain identifying and contact information* as detailed in the study protocol and as permitted under law and by patient consent to enable biospecimen use for longitudinal studies.

4. NCI-supported biorepositories should *establish, as necessary, new policies and protocols* to facilitate the submission of outcome data, ensure uniformity and patient privacy, and track treatment and outcomes.

5. To collect high-quality longitudinal information, NCI-supported biorepositories should require *dedicated and trained personnel* to curate the validation process and QA/QC.

Informatics To Support the Tracking of Data [3]

1. A biorepository informatics system should *track all aspects of biospecimen collection, processing, and distribution* to prevent the confusion of samples and to support annotation.

2. A biorepository should comply with applicable privacy laws, human subjects regulations, and local institutional requirements governing the acquisition of biospecimens and associated clinical data (see the section on Ethical, Legal, and Policy Guidelines for more discussion of clinical data and the protection of patient privacy).

C. Quality Assurance/Quality Control (QA/QC)

NCI-supported biorepositories should develop a formalized QA/QC policy to minimize errors that could adversely affect scientific results. QA/QC policies should be customized for the intended and potential uses of biospecimens in a given biorepository.

QMS

Each biorepository should either establish a written QMS or adhere to one published by the organization with which the biorepository is associated. The QMS should describe the biorepository's QA/QC programs and describe approaches for ensuring that program requirements are met (ISBER 2005). The QMS should describe procedures for conducting audits in the following areas:

1. Equipment maintenance and repair.
2. Training records and adherence of staff to required training schedules.
3. Data management.
4. Recordkeeping.
5. Adherence to SOPs.

SOPs Manual

Each biorepository should develop written policies and procedures in an SOPs manual. The SOPs should state policies and define and describe all procedures in detail.

1. *Contents.* The SOPs manual should specifically include at least the following information:

- Biospecimen-handling policies and procedures, including supplies, methods, and equipment used.
- Laboratory procedures for tests performed in-house and any biospecimen aliquoting or other processing.
- Policies and procedures for shipping and receiving biospecimens, including the MTAs to be used.
- Policies for managing records.
- QA/QC policies and procedures for supplies, equipment, instruments, reagents, labels, and processes employed in sample retrieval and processing.
- Safety programs.
- Emergency safety policies and procedures, including the reporting of staff injuries and exposure to potential blood-borne pathogens.
- Policies and procedures for the investigation, documentation, and reporting of accidents, errors, complaints, and adverse outcomes.
- Policies and procedures and schedules for equipment inspection, maintenance, repair, and calibration.
- Procedures for disposal of medical waste and other biohazardous waste.
- Policies and procedures regarding the training of technical and QA/QC staff members.

2. *Implementation.* The biorepository director and/or the individual responsible for the QA/QC program should review and approve all SOPs and associated process validation studies prior to implementation. Upon implementation, all SOPs must be followed as written.

3. *Modifications.* Each biorepository should have a document control program and policies for governing, modifying, or revising SOPs. Each modification should be approved by the biorepository director or other appropriate individual(s). Implementation dates should be recorded for all procedures. All SOPs should be reviewed every 2 years and have the current date of renewal on the posted copy.

4. *Staff access and review.* Current copies of the SOPs manual should be stored in designated locations and available to the staff at all times. The staff should review new and revised policies and procedures prior to implementation. Documentation of staff review and any associated training should be recorded.

D. Biosafety

Laboratories and biorepositories that handle biospecimens expose their employees to risks involving infectious agents and chemicals, as well as the general dangers of a laboratory. A predictable, yet small, percentage of biospecimens will pose a risk to the biorepository workers who process them. All biospecimens should be treated as biohazards (Grizzle and Fredenburgh 2001). In addition to taking biosafety precautions, biorepositories should adhere to key principles of general laboratory safety.

[2] The NCI plans to partner with its cancer centers, advocacy groups, and relevant stakeholders to collect longitudinal data related to particular studies.

[3] The NCI intends to assist biorepositories in choosing informatics approaches that meet the necessary data tracking and management requirements set forth by the institute.

Biohazard Precautions

Laboratories and biorepositories must assume that all human biospecimens are potentially infective and biohazardous, regardless of whether they are frozen, dried, fixed, processed in paraffin, or otherwise processed. Human biospecimens are defined as blood, other bodily fluids, solid tissues, tissue products, and cell lines. The greatest risks are posed by exposure to the human immunodeficiency virus (HIV), the hepatitis viruses, and the prion that causes Creutzfeldt-Jakob disease, but there are additional significant exposures as outlined by Grizzle and Fredenburgh (2001).

29 CFR 1910.1030 requires that vaccination be offered to all personnel who may be potentially exposed to human blood, body fluids and tissues, or other potentially infectious materials. Biorepository work practices must be based on *universal precautions* practices similar to those used in laboratories and clinical settings. Two basic important safety precautions should be followed in laboratories and biorepositories that handle biospecimens: Wash hands frequently, and always wear face protection and gloves when handling biospecimens or working within or around freezers. Additional good general laboratory work practices are outlined in Table 4 of Grizzle and Fredenburgh (2001).

A biorepository must establish clear *policies regarding the inclusion or exclusion of high-risk* biospecimens. Human biospecimens should be handled according to, at a minimum, BSL–2 as outlined in the CDC/NIH booklet *Biosafety in Microbiological and Biomedical Laboratories* (CDC and NIH 1999). Under BSL–2, when biospecimen containers are opened for processing, they should be handled in a BSL–2 biological safety cabinet (hood). All biorepositories that handle human biospecimens should operate under the OSHA's blood-borne pathogens standard and should develop an exposure control plan (29 CFR 1910.1030). Additional precautions apply, as outlined in the CDC booklet.

Some activities may require higher containment, and in other cases, less stringent practices may be acceptable. Therefore, it is best to ensure that biorepository staff members are trained to perform risk assessments and determine appropriate biosafety levels.

Guidelines

1. Identify governmental and accrediting agency requirements regarding biohazards and likely sources of current information concerning laboratory biosafety for use in developing an overall program in safety and associated training programs. Among the agencies that oversee laboratory biosafety programs are the OSHA and the CLSI. The CDC oversees programs that handle Select Agents.

2. Identify risks and other general issues of biosafety. Identify frequent biorepository activities and analyze safety issues involved with each activity, and implement suitable controls.

3. Improve biosafety by developing written working guidelines that are based on Federal and State requirements, experience, and published information. These guidelines should be reviewed and updated regularly and modified in response to problems or if they prove ineffective.

4. Develop and implement a training program. Each employee should receive training in relevant areas of safety before beginning work, and the training should be updated annually.

5. Record and arrange for treatment for all incidents where personnel are exposed to biohazards or are potentially infected.

General Laboratory Safety

In addition to biosafety, biorepositories need to follow strict general safety regulations and procedures. Recommendations regarding general laboratory safety follow. Additional details and references regarding biorepository safety can be found in the ISBER Best Practices, Section J, and Appendix A (ISBER 2005).

1. *Chemical safety.* Follow U.S. regulations concerning chemical safety, which protect employees from exposure to hazardous levels of chemicals in biorepositories, including, for example, formaldehyde used to fix tissues. Biorepositories should also comply with OSHA regulations governing occupational exposure to hazardous chemicals in laboratories (29 CFR 1910.1450).

2. *Electrical safety.* Freezers and other biorepository equipment must be properly grounded.

3. *Fire safety.* Emergency plans must be in place and practiced on a regular basis. Purchase noncombustible freezers and refrigerators.

4. *Physical safety.* Repetitive strain and back injuries are typical occupational biohazards in the biorepository. Take proper precautions to prevent these and other accidents and injuries typical of the laboratory/biorepository environment.

5. *Radiological safety.* Any laboratory or biorepository that processes radioactive materials requires proper training and equipment to obtain licenses from the NRC and/or local agencies.

E. Biorepository Informatics: Data Management and Inventory Control and Tracking

Driven by advances in genomics and proteomics, informatics systems have become increasingly critical to the research enterprise. Informatics systems that support NCI-sponsored biorepositories must be robust and reliable and able to meet changing needs while remaining interoperable.

An informatics system should support all aspects of biorepository operations, including (but not limited to) patient enrollment and consent; biospecimen collection, processing, storage, and dissemination; QA/QC; collection of patient data; data security; validation documentation; and management reporting functions. The system should also manage clinical annotations to the biospecimens and, where possible, support those patient followup needs permitted by ethical considerations and appropriate regulations. Biorepository systems should also be interoperable with those that house endpoint assay data (*e.g.*, proteomics, genomics) to ensure that integration of data from multiple sources will be possible. The NCICB has developed caBIG (see *https://cabig.nci.nih.gov/*), a voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools. The informatics systems selected or developed for new biorepositories should be caBIG-compatible at the ''silver'' level (see *https://cabig.nci.nih.gov/guidelines_documentation*) with the goal of interoperability with other systems. Where systems for existing biorepositories are being replaced or upgraded, they should also be compatible at the silver level. For existing software, migration paths to silver level compatibility should be identified, with the expectation that this will become a requirement in later versions of these guidelines.

General Informatics Guidelines

1. Each biospecimen should be assigned a unique identifier (number and/or barcode) at the time of collection.

2. Specific clinical and epidemiological data should be identified by the same number and/or barcode.

3. The same number or code should be used to track a biospecimen from

collection through processing, storage, and distribution.

4. The biorepository database should be updated each time the biospecimen is moved within or out of the biorepository.

Functionality of Biorepository Informatics Systems

1. Biorepository informatics management systems should be based on use cases and other domain level modeling techniques (*e.g.*, data or object models) that capture the needs for managing biorepositories. SOPs for the activities carried out in a biorepository should largely drive the design of informatics systems.

2. At the biorepository level, informatics systems should focus on inventory functions, tracking all phases of sample acquisition, processing, handling, QA/QC, and distribution from collection site (patient) to utilization (researcher). Restocking of returned, unused samples from the researcher, if allowed, also must be tracked. Tracking should also include documenting multiple, preexisting, external physical biospecimen identifiers, such as barcodes with non-identifying information.

3. The informatics system must be able to link the information it contains to the physical biospecimen containers via labels on those containers (*e.g.*, paper labels/barcodes).

4. Systems should utilize data elements from a common metadata biorepository, such as the Cancer Data Standards Repository (caDSR, see *http://ncicbsupport.nci.nih.gov/sw/content/caDSR.html*).

5. The informatics system should account for ''legacy'' identifiers and be able to track multiple identifiers and any barcodes generated in the resource.

6. Informatics systems should be able to track clinical data associated with a biospecimen and minimally should support the collection of a ''universal clinical data set.'' The NCI will work with biorepositories to develop this minimal clinical data set to be collected for all biospecimens, as appropriate for the research protocol at NCI-supported biorepositories. This universal data set will change over time. The informatics system should be able to link biospecimen data with external sources of clinical data.

7. Tools used to extract structured information from free-text data, such as surgical pathology reports, should be validated as to their accuracy in performing that task. Biorepositories should routinely monitor the performance of such tools.

8. All NCI-supported biorepository databases at an individual institution should be in a secure site monitored by the institution. All systems should have a backup plan. Biorepositories should eliminate unsecured, *ad hoc* databases, such as those recorded in Excel, Access, and FileMaker Pro, and manage data by the central informatics system. Institutions without the capabilities to provide such infrastructure should seek external hosting arrangements for such a system.

Integration

1. The informatics system at each NCI-supported biorepository should be able to integrate with the host institution's clinical data systems, including the anatomic pathology laboratory information system (AP–LIS), the clinical pathology laboratory information system (CP–LIS), and the Cancer Registry. The NCI is developing the caTISSUE Clinical Annotation Engine to assist in this effort.

2. NCI-supported biorepositories should use informatics systems that support the linking of biospecimens with associated research data (*e.g.*, genomic and proteomic analyses) and, when available, agreed upon limits, if any, on use of the sample. If applicable, NCI-supported biorepositories should track the levels of consent that each patient has given for the use of his or her biospecimens and whether that consent has been withdrawn.

Interoperability

1. Informatics systems at individual NCI-supported biorepositories should be connected through a centralized, enterprise-level framework.

2. Semantic and syntactic standards should be common across the individual bioinformatics systems.

3. While informatics systems at NCI-supported biorepositories will have different informatics requirements based on workflow, systems should be interoperable to integrate clinical and research data and establish distributed tissue resources.

4. NCI-supported biorepositories should support a minimum set of common queries that can be run across all systems using common data elements. In the future, all NCI-supported systems should support queries across multiple systems or biorepository networks.

Development

1. Software and system development methodology should be followed for initial development and subsequent revisions.

2. Software and system engineering organizations should meet at least Capability Maturity Model Integration (CMMI) Level 3 (Carnegie Mellon 2005).

Ethical and Legal Issues [4]

1. An honest broker-guided procedure should be used to protect research participants' privacy for samples and data in all NCI-sponsored biorepositories. The honest broker may be considered a function of the informatics system, not necessarily an individual.

2. The system should allow users to perform only those operations for which they have permission at the object, record, and attribute levels.

3. Permissions and user roles should be defined to ensure proper access to data and biospecimens in compliance with all applicable privacy laws and human subjects regulations (45 CFR part 46). Data about biospecimens should be provided on terms that are not exorbitant, do not grant reach-through rights, or are otherwise not unduly onerous (*i.e.*, are consistent with NIH research tools and data policies—see *http://www.nih.gov/news/researchtools/* and *http://grants1.nih.gov/grants/policy/data_sharing/index.htm*).

4. All existing systems should be mapped to minimal standards (to be defined by NCI), and a timeline should be set for implementation to encourage the adoption of a federated informatics system.

5. NCI-supported biorepositories should meet relevant State and Federal requirements encouraging the use of electronic signatures where appropriate, and IT accessibility standards for handicapped persons.

Assessing Biorepository Informatics Systems

1. Existing or ''legacy'' biorepositories should be evaluated on the basis of their respective levels of informatics capabilities, including the usage of CDEs, access to data through standard queries, data accuracy, and adherence to other stated guidelines.

2. The biorepository informatics system should provide reporting capabilities that allow biorepository managers to monitor its state in terms of the scientific best practices described elsewhere in these guidelines. The system should provide information to those managers to maintain the requisite level of biospecimen quality.

[4] The NCI will develop and implement SOPs for annotating clinical data to accompany samples stored in NCI-supported biorepositories. Informatics systems should be designed to accept these annotations and link them with samples in a deidentified manner.

3. Biorepository informatics systems should be able to provide vital system statistics and audit logs of all access to protected health information in the database.

NCI Infrastructure To Support These Guidelines

The NCI has developed a number of initiatives that may be used to assist its Cancer Centers that wish to implement these guidelines and is currently exploring further mechanisms to assist the community with overall implementation of these recommendations. These initiatives include the caBIG™ (see *https://cabig.nci.nih.gov/*), an infrastructure project designed to facilitate the exchange of data and programs among NCI-supported Cancer Centers. An associated Tissue Banking and Pathology Tools Workspace provides specifically for the needs of biorepositories. As part of this program, the NCI is developing the following components:

1. *caTISSUE Core.* An Intra/internet-based application for managing a biorepository. caTISSUE also provides an object model through which existing biorepository systems may be used as a standard to share biospecimen data.

2. *caTISSUE-Clinical Annotation.* An application for handling the annotation of biospecimens with clinical data.

3. *caTIES.* A system for extracting concepts from free text pathology reports into a structured data model.

The caDSR and its associated services provide the infrastructure to handle the standardized terminologies referred to in the recommendations. caBIG silver-level compatibility is outlined in the caBIG documentation at *https://cabig.nci.nih.gov/guidelines_documentation.*

2. Ethical, Legal, and Policy Guidelines

A. Informed Consent

Informed consent (pursuant to the human subjects regulations at 45 CFR part 46) is designed to present potential human research participants with sufficient information—including anticipated procedures, risks, and benefits—to make an informed decision to participate in research studies. Obtaining informed consent for the collection and storage of biospecimens and for their use in future research is challenging since the specifics of the future research are often not known at the time of biospecimen collection. Despite this challenge, the informed consent information describing the nature and purposes of the research should be as specific as possible. The specific type of research that may be done in the future on donated biospecimens may be sufficiently anticipated and described in the original informed consent to satisfy HHS regulations.

1. The *timing of consent* (*e.g.* before or after surgery) to use specimens for research purposes should not be imposed rigidly, but the donor must be informed by a number of important considerations, including ethical guidelines and logistical constraints.

2. The NCI will provide biorepositories with a *sample consent template*, for example, the NCI Sample Consent Form for Use of Tissue for Research (Appendix 1), which should be adapted to conform to applicable state law and local policy, and approved by the appropriate IRB. Although there should be areas of uniformity across all NCI-supported biorepositories, there should also be some flexibility so that biorepositories can adapt the sample template to their needs.

3. The sample consent forms used by NCI-supported biorepositories should, if appropriate, address the use of biospecimens or data by non-government individuals or entities, the issue of research leading to future development of commercial products, and the release of individual research results to participants.

4. Research participants should be allowed to specify the *types of research* for which their biospecimens may be used, including use in additional future projects.

5. NCI-supported biorepositories should develop policies and procedures to handle biospecimens and associated computer records for which consent has been *withdrawn.* Informed consent documents should highlight the research participant's or source's ability to withdraw consent and describe what will take place should consent be withdrawn.

- In the event that consent is withdrawn for the continued research use of biospecimens, individually identifiable biospecimens and any distributed samples must be withdrawn from the biorepository, and attempts should be made to retrieve samples. In addition, consent can also be withdrawn for the analysis phase of identifiable private information, since it is considered human subjects research. However, a processed sample and the research data generated from it cannot be rescinded.
- In the event that consent is withdrawn, biospecimens should be destroyed or alternatively stripped of all direct and indirect identifiers. However, biorepository managers should be sensitive to cultural issues and should work with affected groups to develop mechanisms for returning or destroying biospecimens. The option of stripping all direct and indirect identifiers from biospecimens should be included in consent forms for subjects who later withdraw consent.

6. NCI-supported biorepositories that house identifiable biospecimens and data from children that are obtained with parental or guardian permission should continually monitor the need for obtaining informed consent when a child reaches the legal age to consent for a research study. If the biospecimens/data are used in studies that require ongoing interactions or interventions with the subject or that continue to meet the regulatory definition of ''human subjects research'' and the child reaches the legal age to consent for new research, this subject's participation in research is no longer regulated by 45 CFR 46.408. A legally effective informed consent should be obtained from the child turned adult subject unless the IRB waives the requirement for obtaining informed consent under CFR 46.116(d).

7. FDA regulations must be considered for research on existing biospecimen collections. These regulations may not exempt *in vitro* studies from the requirement for documented, IRB-approved consent from the sources, even in cases where biospecimens have been deidentified.

8. NCI-supported biorepositories should establish and document transparent *policies governing records and biospecimen retention.* These policies should be made available to participants, either in the informed consent document or in supporting information. In addition, usage agreements with recipient investigators should specify the retention policy of the recipient investigator.

- For clinical biospecimens, the timing is informed by Federal and State laws governing how long records are retained.
- For research biospecimens, the ideal is permanent storage if there are sufficient resources and storage space, subject to reasonable foreseeable research utility (i.e., QA/QC, dated data sets).
- Biorepositories should be reviewed periodically (*e.g.*, at the time of funding renewal) to determine the utility of existing biospecimens, the need for new biospecimens, etc.
- In the event that biorepositories close because of lack of funding or otherwise cannot maintain or use the biospecimens, the availability of the biospecimens for transfer should be

announced to the research community (*e.g.*, via a Web site). The transfer of such biospecimens must be consistent with human subjects regulations.

For additional information about IRBs and the requirement for OHRP-approved assurance of compliance, see the OHRP Web site at *http://www.hhs.gov/ohrp/.*

B. Access to Biospecimens and Data

Access to human biospecimens for research purposes is crucial for fields such as genomics, proteomics, metabolomics, molecular imaging, and nanotechnology. Researchers in these areas often rely on federally funded biorepositories for high-quality biospecimens and associated data.

1. *NCI-funded biorepositories should establish clear guidelines, as the research community's custodian of biospecimens, for sample distribution (and clinical data sharing) consistent with ethical principles, prevailing laws and regulations, and, if applicable, consent form language.* The NCI intends to have a substantial role in developing the best practices on which these guidelines will be based. These guidelines should build on the work of other groups and should be:

- *Clear* to ensure their comprehension and adherence.
- *Flexible* so that biorepositories may be responsive to changing scientific needs.
- *Amendable* to facilitate their adaptability over time.
- *General* enough so they may be applied to different kinds of biorepositories.

In addition, the best practices will delineate when biospecimens (and clinical data) should be narrowly or broadly accessible and what justifications will be expected of funded biorepositories.

2. *Investigators should have timely, equitable, and appropriate access to human biospecimens stored at NCI-supported biorepositories without undue administrative burden.* A prescribed mechanism for rapid turnaround of requests should be in place at NCI biorepositories that (1) relies on a peer (or stakeholder) review system that sets priorities as to how collected biospecimens should be allocated to qualified recipient investigators and (2) ensures that proposed uses are consistent with the participant's consent, research purpose, and allowable use of biospecimens.

- Decisions should be guided by a set of general principles that include:
- Fair and clearly communicated access procedures.
- Protocol-specific requirements that must be met before other access is considered.
- Preference for access to investigators from the protocol coordinating group or NCI-funded investigators before access is granted to others.
- Access granted on the basis of scientific merit with the following criteria:

1. Institutional research qualifications and proven investigator experience with the method proposed.
2. Standardized, validated research biomarker assay methodology.
3. A research plan appropriate to answer the study question.
4. Statistical evaluation which shows that the study question can be addressed with the samples available.
5. The investigator has defined funding and IRB approval for the project.
6. The investigator has defined a study interval and will provide information about the project outcome at the end of that period.
7. The investigator agrees to group publication guidelines.
8. The investigator agrees to make assay data available according to agreed-upon rules.

- Access includes negotiated arrangement with a clinical protocol coordinating group to provide timely statistical analysis of study results.
- Investigator agrees to compensate tissue bank for specimen preparation and shipping and coordinating group statisticians for timely data analysis.
- Provide investigator agreements, principles and process for review.
- Access policies and procedures should apply to all biorepositories and should include the following:

—Investigator agreement covering confidentiality, use, disposition, and security of biospecimens and associated data.
—Investigator's written agreement in a Material Transfer Agreement that complies with the NIH Research Tool Policy. (*http://ott.od.nih.gov/policy/rt_guide_final.html*).
—Appropriate ethical oversight.

- An appropriate model for biospecimen and associated clinical data usage should be based on matching usage with appropriate scientific investigations (*e.g.*, discovery, prevalence, initial validation, hypothesis testing). The level of identifiability of the biospecimen should be appropriate for the proposed research.
- The local decisionmaking body should take local principles into account. Ethical considerations should come first among principles that guide the decisionmaking process.
- Guidelines should apply to all new collections and, whenever possible, to existing collections.
- An appeals process should be established for addressing disputes over allocation decisions.

3. *Charges for samples should be used only to recover costs.* Cost-recovery models, and thus pricing strategies for biorepositories, can vary. If applicable and where monetary charges are necessary, charge only to recover costs as appropriate to retrieve and disseminate specimens.

4. *NCI-supported biorepositories should use a system of data access with defined levels of access privileges.*

- Access levels should be described in the protocol for operation of the biorepository, as well as in the informed consent form, and should be approved by an IRB and/or bioethics-scientific advisory board.
- Access to research participants' identities and medical, genetic, social, and personal histories should be restricted to only those biorepository staff members who need to access such records as part of their assigned duty or to those persons permitted access by law.
- The number of personnel allowed to access links and reidentify information should be kept to a minimum, and access should be appropriately monitored to ensure compliance.

5. *NCI-supported biorepositories should store human biospecimens for research purposes only and should not serve an individual research participant's needs or wishes.*

C. Privacy Protection

Research depends on protecting the privacy of individuals who contribute biospecimens to biorepositories and on maintaining the confidentiality of associated clinical data and information (Eiseman *et al.* 2003). Applying the highest possible ethical standards is necessary to ensure the support and participation of patients, physicians, researchers, and others in biorepository activities (*NBN Blueprint* 2003). With the recent advances in genomic and proteomic technology, the sequencing of the human genome, and the increasing reliance by biorepositories on electronic and web-based databases to track data, it is even more crucial to address the risk of unintended release or disclosure of sensitive information, which can place individuals at risk for discrimination and related groups at risk for stigmatization.

1. NCI-supported biorepositories should establish clear policies for protecting the privacy of information. These policies may include data encryption, coding, and establishing limited access or varying levels of access to data by biorepository employees.

2. In applications for support, biorepositories should document their policies, describe mechanisms for auditing effectiveness and for enforcement, describe required training, and specify security measures pertaining to employee access to data and biospecimens.

3. The level of security should be appropriate to the type of biorepository.

D. Custodianship

1. *NCI-supported biorepositories should propose plans for formal and continuing responsibility for custodianship (not ownership*[5]*) of collected biospecimens and associated data as part of the biorepository protocol.* Biorepositories should address this issue in applications for funding, specifically, (a) How does the biorepository propose to ensure the physical integrity of biospecimens? (b) How does the biorepository propose to ensure the integrity of the patient data that accompany the biospecimens? (c) What plans and protocols exist for the distribution of samples to investigators? (Also see Access to Biospecimens and Data, section B.2 above.)

2. *Biorepositories should address plans for the handling and disposition of biospecimens and associated data at one or more of the following points:* (a) End of the budget period of the grant, (b) accomplishment of the specific research objectives of the study, (c) depletion of biospecimens, or (c) achievement of critical data endpoints.

3. Individuals responsible for allocating biospecimens or associated data from biorepositories should *disclose financial or professional conflicts of interest* to existing conflict-of-interest committees in the host institution or to the biorepository's governing board.

[5] The issue of ownership of biospecimens, associated data, and research findings remains ambiguous and controversial, partly because of wide variation and lack of harmonization in the regulatory and legal standards used by courts, state legislatures, and Federal regulators in determining ownership rights. The end result has been the use of unclear or misleading legal language in informed consent and other documents that does not adequately address the issue of ownership, by either the individual who is the source of the biospecimen, the principal investigators who collect and bank the biospecimens, the recipient investigators who use the samples for research purposes, or the biorepository and its host institution.

4. NCI-supported biorepositories should use *clear and specific informed consent language* to ensure that those who contribute biospecimens and/or data for research purposes are fully informed that the research done with these biospecimens may help to develop products, tests, or discoveries that may have commercial value (see sample template, Appendix 1).

E. Intellectual Property

Inventions arising from research using annotated biospecimens may have commercial value. As researchers and industry sponsors have sharply increased their demand for properly prepared and clinically annotated biospecimens, some institutions have begun to assert control over biospecimens, associated data, and research findings. The current variability in IP policies at institutions hosting NCI-supported research and biorepositories may ultimately lead to problems in biospecimen and data access, timely and open publication, sharing of research findings, and establishment of new biorepositories.

1. For the transfer of materials in academic-industrial collaborations, use the NIH SLA, the UBMTA, or other MTA with terms consistent with the NIH Research Tools Policy and NIH data sharing policies. The above agreements should be modified where necessary to cover human subjects research. A sample NIH SLA modified to address the transfer of human biospecimens is attached as Appendix 2.

The following Internet sites are relevant to this issue:

- *http://ott.od.nih.gov/policy/research_tool.html.*
- *http://www.autm.net/aboutTT/aboutTT_umbta.cfm.*
- *http://grants1.nih.gov/grants/policy/data_sharing/index.htm.*

2. Recognize that biorepository staff members as custodians of biospecimens are not *a priori* considered inventors under patent law for inventions made using materials distributed by the biorepository. In general, the staff should be informed that one whose sole contribution to an invention consists of the routine collection, handling, storage, and disbursement of biospecimens might not rise to the level of ''inventor'' of an invention. Inventorship is determined by patent law and must be considered on a case-by-case basis by trained legal personnel.

3. Recognize that biorepositories have no inherent rights to future IP, such as reach-through rights in inventions made by investigators using samples obtained from the biorepository.

4. Ensure through appropriate MTAs that research data obtained using biospecimens are made available to the research community, consistent with NIH data sharing policies such as the Final NIH Statement on Sharing Research Data (*http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html*).

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Appendix 1—NCI Sample Consent Form for Use of Tissue for Research

The following tissue consent example has been adapted from the NCI Cancer Diagnosis Program's sample consent form, also available at: *http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf.* The accompanying instruction sheet can be found at *http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf.*

_____

Name of Tissue Repository

_____

_____

Address and phone number

Consent Form for Use of Tissue for Research

About Using Tissue for Research

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called ''How Is Tissue Used for Research?'' to learn more about tissue research.

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things To Think About

The choice to let us keep the leftover tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue.

Then any tissue that remains will no longer be used for research. However, once knowledge is gained from a sample, that knowledge cannot be taken back.

In the future, people who do research may need to know more about your health. While the [*INSERT ORGANIZATION NAME*] may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for familial or hereditary genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. However, the research done with your tissue may help develop new products, tests, or discoveries in the future, which may have commercial value. The [*INSERT ORGANIZATION NAME*] does not plan to share any commercial profits with you.

Benefits

There will be no direct benefit to you, financially or otherwise, by participating in this research study.

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. The chance that this information will be given to someone else is very small.

Making sure that your identity does not become known will minimize the chance that you will experience any psychological or social harm. Therefore, we will take every precaution to safeguard your identity. As soon as it is collected, your tissue and your clinical information will be assigned a code number. That code number will be the only information attached to your samples and clinical information. All other widely used identifying information, such as your name, address, phone number, and Social Security number will be removed. The master list, which will link your name and the code number, will be kept under lock and key and in a computer with electronic safeguards. Only authorized people who have agreed in writing to protect your identity will have access to your linked information. Therefore, the researchers and others working with your samples and clinical information will not know your identity.

Your privacy is very important to us. However, in spite of these safety measures, we cannot guarantee that your identity will never become known. Due to scientific advances or human errors, your identity could become known. Since your DNA information is unique to you, in the future it may become possible for someone to identify you. This would require someone to take another tissue sample from you, analyze the DNA, and compare it with data resulting from this research project. Currently, this risk is very slight.

If your identity were ever determined, this might cause you and your family some distress. In addition, if it became known that you have disease-causing DNA changes, there is a very small risk that you might have a harder time getting or keeping a job or health insurance. Some laws exist that attempt to protect people from such job and insurance discrimination. However, these laws may not fully protect people from discrimination.

Since you share genetic characteristics with your children, parents, brothers, sisters, and other family members, it is possible that some of these risks may apply to them as well. However, their risks are likely to be even lower than yours, since it will be even more difficult to identify them than to identify you.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle ''Yes'' or ''No.'' No matter what you decide to do, it will not affect your care. If you have any questions, please talk to your doctor or nurse or call our research review board at [IRB's phone number]. If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue for research

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.

Yes No

2. My tissue may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. My medical record information may be associated with research on my tissue.

Yes No

4. Someone from the [INSERT ORGANIZATION NAME] may contact me in the future to ask me to take part in more research.

Yes No

Please sign your name here after you circle your answers.

Your Signature: _____

Date: _____

Signature of Doctor/Nurse: _____

Date: _____

How Is Tissue Used for Research?

(This information brochure is to be distributed with the informed consent document.)

Where does tissue come from?

Whenever a biopsy (or surgery) is performed, the tissue that is removed is examined under the microscope by a trained doctor to determine the nature of the disease and assist with the diagnosis. Your tissue will always be used first to help make

decisions about your care. After all tests have been done, there is usually some leftover tissue. Sometimes, this tissue is not kept because it is not needed for the patient's care. Instead, a patient can choose to have the tissue kept for future research. People who are trained to handle tissue and protect the donor's rights make sure that the highest standards are followed by the [*INSERT ORGANIZATION NAM*E]. Your doctor does not work for the [*INSERT ORGANIZATION NAME*] but has agreed to help collect tissue from many patients. Many doctors across the country are helping in the same way. If you agree, only leftover tissue will be saved for research. Your doctor will take only the tissue needed for your care during surgery.

Why do people do research with tissue?

Research with tissue can help find out more about what causes cancer, how to prevent it, and how to treat it. Research using tissue can also answer other health questions. Some of these include finding the causes of diabetes and heart disease or finding genetic links to Alzheimer's.

What type of research will be done with my tissue?

Many different kinds of studies use tissue. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help develop new products, such as tests and drugs.

Some research looks at diseases that are passed on in families (called familial or hereditary genetic research). Research done with your tissue may look for genetic causes and signs of disease.

How do researchers get the tissue?

Researchers from universities, hospitals, and other health organizations conduct research using tissue. They contact the [*INSERT ORGANIZATION NAM*E] and request samples for their studies. The [*INSERT ORGANIZATION NAME*] reviews the way that these studies will be done, and decides if any of the samples can be used. The [*INSERT ORGANIZATION NAME*] gets the tissue and information about you from your hospital and sends the tissue samples and some information about you to the researcher. The [*INSERT ORGANIZATION NAME*] will not send your name, address, phone number, Social Security number, or any other identifying information to the researcher.

Will I find out the results of the research using my tissue?

No, you will not receive the results of research done with your tissue. This is because research can take a long time and must use tissue samples from many people before results are known. Results from research using your tissue may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Though research involves the test results of many different people, your biopsy result involves only you. Your doctor will give you the results of your biopsy when results are known. These test results are ready in a short time and will be used to make decisions about your care.

Will I benefit from the research using my tissue?

There will be no direct benefit to you, financially or otherwise. However, it is hoped that the results of research on your tissue and tissues from other patients will provide information that will help other patients in the future. Your tissue will be helpful whether you have cancer or not.

Why do you need information from my health records?

In order to do research with your tissue, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher includes your age, sex, race, diagnosis, treatments, and possibly some family history. This information is collected by your hospital from your health record and sent to the [INSERT ORGANIZATION NAME] but without your name or other identifying information. If more information is needed, the [INSERT ORGANIZATION NAME] may send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number, and anything else that could identify you will be removed before the other information goes to the researcher.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may apply not only to you but also to your family members. For diseases caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The [INSERT ORGANIZATION NAME] is in charge of making sure that information about you is kept private. The [INSERT ORGANIZATION NAME] will take careful steps to prevent misuse of records. Your name, address, phone number and other identifying information will be taken off anything associated with your tissue before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person, which will help protect your privacy.

Making sure that your identity does not become known will minimize the chance that you will experience any psychological or social harm. Therefore, we will take every precaution to safeguard your identity. As soon it is collected, your tissue and your clinical information will be assigned a code number. That code number will be the only information attached to your samples and clinical information. All other widely used identifying information, such as your name, address, phone number, and Social Security number, will be removed. The master list, which will link your name and the code number, will be kept under lock and key and in a computer with electronic safeguards. Only authorized people who have agreed in writing to protect your identity will have access to your linked information. Therefore, the researchers and others working with your samples and clinical information will not know your identity.

Your privacy is very important to us. However, in spite of these safety measures, we cannot guarantee that your identity will never become known. Due to scientific advances or human errors, your identity could become known. Since your DNA information is unique to you, in the future it may become possible for someone to identify you. This would require someone to take another tissue sample from you, analyze the DNA, and compare it with data resulting from this research project. Currently, this risk is very slight.

If your identity were ever determined, this might cause you and your family some distress. In addition, if it became known that you have disease-causing DNA changes, there is a very small risk that you might have a harder time getting or keeping a job or health insurance. Some laws exist that attempt to protect people from such job and insurance discrimination. However, these laws may not fully protect people from discrimination.

Since you share genetic characteristics with your children, parents, brothers, sisters, and other family members, it is possible that some of these risks may apply to them as well. However, their risks are likely to be even lower than yours, since it will be even more difficult to identify them than to identify you.

Appendix 2—Material Transfer Agreement for Human Biospecimens

Provider Organization (''Provider''): _____

Recipient Organization (''Recipient''): _____

1(a). The material to be transferred (''MATERIAL'') (Name or description of human Biospecimen(s) or Collection, Method of Preservation, Organ Source, etc.):

_____

_____

1(b). Designate the Private Identifiable Information status of the MATERIAL (Please see Annex A for definitions) (check one below):

____Unidentified specimens

____Unidentified or ''anonymous'' samples

____Unidentifiable

____Coded specimens

____Coded samples

2. The Recipient will use the MATERIAL (check one only):

____As a biorepository that will distribute the MATERIAL to the research community on behalf of the Provider under a separate Material Transfer Agreement.

____To conduct an independent research project (Describe the ''RESEARCH PROJECT'' below):

Recipient Serving as a Biorepository

3. If the MATERIAL is being provided by the Provider under this Agreement for the purpose of the Recipient distributing the MATERIAL to the research community, the Provider hereby grants the Recipient explicit permission to further distribute the MATERIAL to the research community as a biorepository. Provider Approval (initial here) _____
4. If the Recipient is designated as a biorepository in Article 2, the Recipient is the custodian of the MATERIAL and therefore does not by virtue of this Agreement acquire any intellectual property rights in the MATERIAL, nor in any research conducted by third-parties using the MATERIAL.
5. The MATERIAL will be distributed by Recipient in compliance with all applicable statutes and regulations.

Recipient Conducting an Independent Research Project

6. If the MATERIAL is being provided by the Provider under this Agreement for the purpose of the Recipient conducting an independent research project, the MATERIAL will be used in compliance with all applicable statutes and regulations. The MATERIAL was collected and is provided in accordance with appropriate Federal and local laws, Assurances, and Institutional Review Board approvals related to Human Subjects Research. Recipient is responsible for obtaining any necessary Human Subjects research approvals or exemptions required to use the MATERIAL for the RESEARCH PROJECT.
7. The Recipient will not further distribute the MATERIAL to others who are not under the Recipient Scientist's direct supervision without written consent from the Provider. The Recipient shall refer any request for the MATERIAL to the Provider.
8. The Recipient will in no way attempt to identify or contact the person(s) associated with the biospecimen(s) that make up the MATERIAL. Furthermore, Recipient will not attempt to obtain or otherwise acquire any private identifiable information associated with the biospecimen(s) that make up the MATERIAL under this Agreement. The MATERIAL will be coded or otherwise deidentified. Any widely used identifying information will have been removed. However, it is acknowledged that, due to scientific advances such as DNA analyses or human errors, there is a small risk that the identity of the person who was the source of the MATERIAL could become known.
9. It is intended that Recipient publish the results of the RESEARCH PROJECT and make the associated data available to the research community in a manner consistent with the NIH data sharing policies found at *http://grants1.nih.gov/grants/policy/data_sharing/index.htm.* The Recipient agrees to acknowledge the source of the MATERIAL in any publications or disclosures reporting use of it.
10. Recipient retains ownership of intellectual property made by its employees using the MATERIAL as part of the RESEARCH PROJECT to the extent permitted by law or contractual agreements.

All Parties Agree

11. THIS MATERIAL IS NOT FOR USE IN HUMAN SUBJECTS.
12. The above MATERIAL is being distributed as a service to the research community. It is acknowledged that the MATERIAL is a nonrenewable research resource and that further distribution for research purposes may be determined by scientific merit of the proposed research project. Accordingly, the MATERIAL will be made available to other scientists under a separate Material Transfer Agreement for scientifically approved projects and to the extent supplies are available.
13. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE 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 WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Unless prohibited by law, the Recipient assumes all liability for claims for damages against it by third parties that may arise from its use, storage, or disposal of the MATERIAL, except that, to the extent permitted by law, the Provider shall be liable to the Recipient when the damage is caused by the gross negligence or willful misconduct of the Provider.

Signatures for Provider

Provider Scientist: _____

Provider Organization: _____

Address: _____

Name of Authorized Official: _____

Title of Authorized Official: _____

Signature of Authorized Official

Date: _____

Certification of Provider Authorized Official: This Agreement__has/__has not been modified. If modified, the modifications are attached.

Signatures for Recipient

Recipient Scientist: _____

Recipient Organization: _____

Address: _____

Name of Authorized Official: _____

Title of Authorized Official: _____

Signature of Authorized Official

Date: _____

Certification of Recipient Scientist: I have read and understood the conditions outlined in this Agreement, and I agree to abide by them in the receipt and use of the MATERIAL.

Scientist Receiving Material

Date: _____

Annex A

Definitions (applicable to Appendix 2)

Coded samples: Sometimes termed ''linked'' or ''identifiable,'' these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information, such as a name or Social Security number.

Coded specimens: Sometimes termed ''linked'' or ''identifiable,'' these specimens are supplied by repositories to investigators with a code rather than with personally identifying information, such as a name or Social Security number.

Unidentifiable: Tissue for which identifiable information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.

Unidentified or ''anonymous'' samples: Samples supplied by repositories to investigators from a collection of unidentified human biological specimens and can never be traced to an individual. Unlinked or ''anonymized'' samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being but may have been derived from an identified sample in the repository.

Unidentified specimens: For these specimens, identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.

IV. Implementation

A. Date of Implementation

The adoption of these guidelines is voluntary. However, the NCI may consider making these guidelines terms and conditions of awards.

B. Roles and Responsibilities

These guidelines will eventually apply to all applicants of NCI-supported biomedical research involving biorepositories of human biospecimens. Certain individuals and groups have special roles and responsibilities with regard to the adoption and implementation of these guidelines.

The NCI staff will provide educational opportunities for the extramural and intramural community concerning these guidelines; monitor its implementation during the development, review, award and conduct of research; and manage the NCI research portfolio to address these guidelines.

1. Principal Investigators

The principal investigator and the applicant institution should address the

inclusion of the guidelines in each application and proposal. Applicants should provide a statement of compliance in each area relevant to their studies where such information is not already provided.

2. Institutional Review Boards (IRBs)

As the IRBs implement the guidelines, the use of the ''NCI Sample Consent Form for Use of Tissue for Research,'' adapted to conform with applicable state law and local policy, and the ''Material Transfer Agreement for Human Biospecimens,'' are strongly encouraged in future applications.

3. Peer Review Groups

In conducting peer review for scientific and technical merit, appropriately constituted initial review groups (including study sections), technical evaluation groups, and intramural review panels will evaluate the proposed plan for the inclusion of the guidelines. Where the guidelines have not been adopted or implemented, the peer review should evaluate the impact on the quality of the biospecimens collected, stored, and or analyzed.

4. National Cancer Advisory Board (NCAB)

The NCAB has approved these guidelines in their draft form, in the interest of ensuring sufficient biospecimens of documented quality to support NCI-sponsored research and the findings that guide the scientific policy of the NCI. Modifications to these guidelines will be considered in light of the overall NCI policy and available scientific data.

5. Extramural Program Staff

NCI Extramural Program staffs are familiar with the scientific merits and capabilities of the sponsored researchers. Staff understanding of the guidelines and their rationale will be essential in assisting in a balanced and rational implementation by sponsored researchers.

6. NCI Director

The NCI Director may recommend modifications to the guidelines based on subsequent information.

7. Educational Outreach by NCI To Inform the Professional Community

NCI-sponsored researchers are located and operate within a wide variety of facilities, including pathology laboratories, surgical practices, comprehensive cancer treatment centers, and clinical or basic research laboratories. The guidelines as published by the NCI are not intended to substitute, supersede, or otherwise replace existing requirements but to be a complement to these requirements and to be applied in the absence of guidelines.

8. Applicability to Foreign Research Involving Human Subjects

For foreign awards, the NCI guidelines for research conducted outside the U.S. are the same as those for research conducted in the United States. Where local laws or regulations differ, investigators should provide the NCI with a rationale for alternate approaches.

V. Abbreviation Definitions Used in these Guidelines

Abbreviation	Definition
caBIG	cancer Biomedical Informatics Grid
caDSR	cancer Data Standards Repository
caTIES	cancer Text Information Extraction System
caTISSUE ...	component of the NCI cancer Biomedical Informatics Grid
CDC	Centers for Disease Control and Prevention
CDEs	common data elements
CFR	Code of Federal Regulations
CHTN	Cooperative Human Tissue Network
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical and Laboratory Standards Institute (formerly NCCLS, National Committee for Clinical Laboratory Standards)
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
GSA	General Services Administration
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IATA	International Air Transport Association
ICAO	International Civil Aviation Organization
IRB	institutional review board
ISBER	International Society for Biological and Environmental Repositories
MTA	Material Transfer Agreement
NBN	National Biospecimen Network
NCAB	National Cancer Advisory Board
NCI	National Cancer Institute
OBBR	Office of Biorepositories and Biospecimen Research (at the NCI)
OHRP	Office for Human Research Protections
OSHA	Occupational Safety and Health Administration
PI	packaging instruction
QA	quality assurance
QC	quality control
QMS	quality management system
SLA	Simple Letter of Agreement
SOPs	standard operating procedures
UBMTA	Uniform Biological Material Transfer Agreement

NCI Glossary of Terms for Purposes of These Guidelines

Accident. Any occurrence that deviates from SOPs or applicable government laws and regulations during specimen retrieval, processing, labeling, storage, or distribution that may affect subsequent use of those specimens (ISBER 2005).

Adverse outcome. An undesirable effect or untoward complication consequent to or reasonably related to specimen integrity (ISBER 2005).

Aliquot. A portion of a specimen that has been divided into separate, smaller parts, usually liquid, which are typically stored in separate containers as individual samples. The term aliquot may also be used as a noun to denote a single sample (ISBER 2005).

Annotation. Explanatory or extra information associated with a particular biospecimen. Annotations may be added by either the pathologist or the resource collector.

Audit. A documented review of procedures, records, personnel functions, equipment materials, facilities, and/or vendors to evaluate adherence to written SOPs or government laws and regulations (ISBER 2005).

Bioinformatics. Research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral, or health data, including those to acquire, store, organize, archive, analyze, or visualize such data (as defined by the NIH Biomedical Information Science and Technology Initiative Consortium (*http://www.bisti.nih.gov/CompuBioDef.pdf*) (Eiseman *et al.* 2003)).

Biorepository. A place, room, or container where biospecimens are stored. Biorepositories vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer.

Biorepository informatics system. The software, hardware, written documents, support, and training that are necessary to annotate, track, and distribute biospecimens within a biorepository or biorepositories.

Biospecimen or specimen. A quantity of tissue, blood, urine, or other biologically derived material used for diagnosis and analysis. A single biopsy may generate several specimens, including multiple paraffin blocks or frozen specimens. A specimen can include everything from subcellular structures (DNA) to cells, tissue (bone, muscle, connective tissue, and skin), organs (*e.g.*, liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, and placenta).

caBIG (cancer Biomedical Informatics Grid). A voluntary network or grid connecting individuals and institutions to enable the sharing of data and tools, creating a World Wide Web of cancer research. The goal of this project is to speed the delivery of innovative approaches for the prevention and treatment of cancer. caBIG is being developed under the leadership of the NCI Center for Bioinformatics. Nearly 500 people from approximately 50 NCI-designated Cancer Centers and other organizations are working collaboratively on over 70 projects in a 3-year pilot project. For more information on caBIG, visit *http://cabig.nci.nih.gov.*

caDSR (cancer Data Standards Repository). The standards repository that hosts CDEs developed by various NCI-sponsored

organizations. caDSR components are instrumental in the collection of metadata associated with clinical trials. caDSR tools facilitate the search and retrieval of CDEs and caDSR is the single, authoritative source of common data.

caTIES (cancer Text Information Extraction System). A project that will focus on two important challenges of biomedical informatics; namely, information extraction from free text and access to tissue. Specifically, caTIES has three primary goals: (1) Extract coded information from free-text surgical pathology reports using controlled terminologies to populate caBIG-compliant data structures, (2) provide researchers with the ability to query, browse, and acquire annotated tissue data and physical material across a network of federated sources, and (3) pioneer research for distributed text information extraction within the context of caBIG. caTIES modules will be developed as generalized components available on the caBIG, in order to facilitate reuse by other caBIG projects requiring tissue information extraction.

caTISSUE. A modular, open-source specimen inventory and tracking system that will encompass a core database module for those Centers in need of new solutions, as well as application programming interfaces (APIs), software development toolkits (SDKs), and additional annotation modules for those centers with legacy systems that wish to link into the virtual tissue repositories and query across Cancer Centers. The caBIG Tissue Banks and Pathology Tools Workspace (TBPTW) is responsible for the release of caTISSUE.

Clinical data. Data pertaining to or founded on actual observation and treatment of patients.

Clinical trial research. Research studies that evaluate new interventions, drugs, or medical therapies given to human research participants in strictly scientifically controlled settings. The purpose of such trials is to determine whether one or more screening, prevention, and/or treatment options are safe, effective, and better than current standard care.

Code of Federal Regulations (CFR). The Code of Federal Regulations is a publication that codifies the general and permanent rules published in the **Federal Register** by the executive departments and agencies of the Federal Government. It is published by the Office of the Federal Register, National Archives and Records Administration, Washington, DC (ISBER 2003).

Coded samples. Sometimes termed ''linked'' or ''identifiable,'' these samples are supplied by biorepositories to investigators from identified specimens with a code rather than with personally identifying information, such as a name or Social Security number.

Collection. See *Retrieval.*

Common Data Elements (CDEs). CDEs standardize metadata between a series of software systems. Such standardization ensures that the same meaning of words is used and that data model and application components are reusable. In addition, it eases the integration of systems.

Confidentiality. A principle emergent from a relationship in which something about an individual, information, or material has been shared (with some degree of loss of privacy) in confidence (*NBN Blueprint* 2003).

Container. Enclosure for one unit or units of specimen(s) (ISBER 2005).

Cooperative Human Tissue Network (CHTN). A six-division, decentralized, NCI-funded, infrastructure that provides biomedical researchers with access to human tissue. Established in response to a Request for Applications in 1987, the CHTN has provided more than 500,000 high-quality tissue biospecimens from a variety of organs to more than 1,000 investigators for the conduct of basic and developmental cancer research. Eighty percent of these researchers are from academic or government institutions; only 20 percent of users are from industry.

Cryoprotectant. An additive that serves to minimize osmotic imbalances that occur with the progression of freezing fronts through a substance and is intended to limit the amount of cell damage due to cell shrinkage and intracellular ice formation (ISBER 2005).

Custodianship. Relates to the caretaking responsibility for the specimen collection, including management and documentation, as well as rights to determine the conditions under which the specimens are accessed and used.

Data. Values derived from scientific experiments or diagnostic procedures organized especially for scientific analysis in a numerical form suitable for processing by computer (*NBN Blueprint* 2003).

Data Sharing Policy (NIH Data Sharing Policy). ''NIH believes that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. NIH endorses the sharing of final research data to serve these and other important scientific goals and expects and supports the timely release and sharing of final research data from NIH-supported studies for use by other researchers. ''Timely release and sharing'' is defined as no later than the acceptance for publication of the main findings from the final data set. Effective with the October 1, 2003 receipt date, investigators submitting an NIH application seeking $500,000 or more in direct costs in any single budget period are expected to include a plan for data sharing or state why data sharing is not possible'' (Grants Policy Statement, 12/03). The NIH Data Sharing Policy is not itself a requirement to share data but rather to have a plan to address sharing of data or to state why sharing is not possible. (NIH Grants Policy Statement Web site *http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm*).

Deidentified protected health information. Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. Such information is not individually identifiable health information (45 CFR 164.514(a)-(c)) (Eiseman *et al.* 2003).

Demographic data. Data relating to statistical characteristics of human populations (*e.g.*, age, gender).

Deviation. An intentional or unintentional event that is a departure from a procedure or a normal practice (ISBER 2005).

Disposition. Final destination of specimens (ISBER 2005).

Distribution. A process that includes receipt of request for specimens, selection of appropriate specimens, and final inspection, in conjunction with subsequent shipment and delivery of specimens to another biorepository, specimen collection center, or laboratory (ISBER 2005).

Dry ice. Solid-phase carbon dioxide.

Genomics. The study of genes and their function; the study of all or a substantial portion of the genes of an organism as a dynamic system, over time, to determine how those genes interact and influence biological pathways, networks, and physiology.

Honest broker. A neutral intermediary between the individual whose tissue and data are being studied and the researcher. The honest broker collects and collates pertinent information regarding the tissue source, replaces identifiers with a code, and releases only coded information to the researcher (Eiseman *et al.* 2003).

Human subject. A living individual about whom an investigator, either professional or student, conducting research obtains (1) Data through intervention or interaction with the individual or (2) identifiable private information (45 CFR 46.102(f)). A Human subject may also be a patient, but is not necessarily one.

Indemnification. A legal term of art meaning to secure a person or entity against hurt, loss, injury, or other damages suffered.

Informatics. The use of science, computer science, information technologies, and other technologies to provide data, information, and knowledge to an individual or an organization. The term is synonymous with information science. See also *biorepository informatics system.*

Informatics system. Refers to the software, hardware, written documents, support, and training necessary to annotate, track, and distribute biospecimens within a biorepository or biorepositories.

Informed consent. An educational process between the investigator and the prospective subject (or the subject's legally authorized representative) as a means to ensure respect for persons; mutual understanding of research procedures, risks, rights, and responsibilities; and continuous voluntary participation (*NBN Blueprint* 2003).

Institutional review board. A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research.

Intellectual property. Creative ideas and expressions of the human mind that have commercial value and receive the legal protection of a property right. The major legal mechanisms for protecting intellectual property rights are copyrights, patents, and trademarks. Another form of protection for data sets available in Europe and most of the industrialized world, except the US, is called ''*sui generis* rights in data.'' Intellectual property rights enable owners to deny some parties or persons from access and use of the property and thus to protect it from unauthorized use.

Interoperability. The ability of two or more systems or components to exchange

information and to use the information that has been exchanged.

Invention. A new and useful process, machine, manufacture or composition of matter, or any new and useful improvement, finding, or product that advances the state of the art or practice and may be patentable.

Label. Any written, printed, or graphic material on or affixed to a specimen container or package (ISBER 2005).

Liquid nitrogen dry shipper. A container used for sending samples in the vapor phase of liquid nitrogen (ISBER 2005).

Longitudinal data. Clinical data acquired over the course of time.

Material Transfer Agreement (MTA). A binding legal agreement between the provider of research materials and the recipient of the materials that sets forth conditions of transfer and use, protects proprietary interests, and restricts distribution of the material. An important aspect of the MTA is that it normally removes liability on the part of the provider that might arise from recipient's use of the research material.

Package. A labeled carton, receptacle, or wrapper containing one or more containers and accompanying labeling material (ISBER 2005).

Paraffin-embedded. Tissue that is formalin fixed and then embedded in wax. (**Note:** Other alternative fixation methods may be used to fix the tissue.)

Patent. A property right granted by the Federal Government or a Sovereign State to an inventor. In order to be patentable, an invention must contain an idea that serves some utility, is novel, and is patentable as defined under U.S. Patent Law.

Patient. A person undergoing medical treatment.

Preservation. Use of chemical agents, alterations in environmental conditions, or other means during processing to prevent or retard biological or physical deterioration of a specimen (ISBER 2005).

Prevalence. Number of cases of a disease, infected persons, or persons with some other attribute present during a particular interval of time.

Privacy. The state or condition of limited access to an individual and/or to information about that individual.

Procedure. A series of steps designed to result in a specific outcome when followed in order (ISBER 2005).

Process validation studies. The process of demonstrating that a specific procedure will consistently produce expected results within predetermined specifications (ISBER 2005).

Processing. Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen to inventory and labeling (ISBER 2005).

Prospective. When an intervention of interest is performed and all relevant information and observations on its effects are gathered after entry into the study. By contrast, ''retrospective'' studies focus on information that has already been collected.

Protected health information (PHI). Any health information that is collected by a covered entity and is individually identifiable (*NBN Blueprint* 2003). Also, a subset of individually identifiable information that can be disclosed only under the following conditions: (1) The use or disclosure is sought solely to review PHI as necessary to prepare the research protocol or other similar preparatory purposes, (2) no PHI is removed from the covered entity during review, and (3) the PHI that the researcher seeks to use or access is necessary for the research purposes. PHI can be deidentified by removing all 18 identifiers listed in section 164.514(b)(2) of the Federal regulations or by having a qualified statistician perform an analysis stating that the risk of the information being used is small (ISBER 2005).

Proteomics. The study of the full set of proteins encoded by a genome; the study of the identities, quantities, structures, and biochemical and cellular functions of all proteins in an organism, organ, or organelle and how these properties vary in space, time, and physiological state.

Quality assurance (QA). An integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project. Same as quality management system (QMS) (ISBER 2005).

Quality control (QC). Specific tests defined by the QA or QMS Program to be performed to monitor procurement, processing, preservation and storage, specimen quality, and test accuracy. These may include but are not limited to performance evaluations, testing, and controls used to determine accuracy and reliability of the biorepository's equipment and operational procedures as well as monitoring of the supplies, reagents, equipment, and facilities (ISBER 2005).

Quality management system (QMS). Same as *Quality assurance (QA)* (ISBER 2005).

Quality. Conformance of a specimen or process with preestablished specifications or standards (ISBER 2005).

Reach-through provisions. Material transfer agreements do not usually require financial payments at the time of the transfer, but many allow the provider to either own, or license exclusively, or obtain payments upon the sale of, developments that the recipient makes with the provider's materials. These are loosely termed ''reach-through'' provisions and are considered by many providers to be desirable because they allow the provider to obtain rights in subject matter to which the provider would not otherwise have rights through its ownership or patent coverage of the material alone. Reach-through provisions are considered undesirable by many recipients because they burden all the developments created after the use of the material and because they are seen as providing an unfairly high level of compensation to the provider for use of the material.

Repository. See *Biorepository,* above.

Research. Systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Retrieval. The removal, acquisition, recovery, harvesting, or collection of specimens (ISBER 2005).

Safety. Processes, procedures, and technologies to ensure freedom from danger or harm.

Sample. Portions of specimens distributed to researchers (Eiseman *et al.* 2003).

Semantics. Refers to the ways that information in a data file should be interpreted by others.

Shipping manifest. A written description of the contents of the shipped package (ISBER 2005).

Simple Letter of Agreement. A short form of a standard material transfer agreement.

Specimen. A portion of tissue, blood, urine, or other material used for diagnosis and analysis. A single biopsy may generate several *specimens,* including a number of slides, paraffin blocks, and/or frozen specimens. See *Biospecimen.*

Standard operating procedures (SOPs) manual. A group of standard operating procedures detailing the specific policies of a biorepository and the procedures used by the staff/personnel (ISBER 2005).

Storage. Maintenance of specimens for future use.

Tissue. Refers generally to a biologic collection of cells, and the extracellular matrix and/or intercellular substances surrounding them. Tissue is most often referred to in the context of solid tissue, as originating from a solid organ; however, tissue can also be defined broadly to include collections of cells and intercellular substances from bodily fluids such as blood.

Tissue Banks and Pathology Tools Workspace (TBPTW). As one of three caBIG pilot domain workspaces, the goal of the TBPTW is to develop a set of tools to inventory, track, mine, and visualize tissue samples and related information from a geographically dispersed biorepository. This Workspace provides an opportunity to bind Cancer Center systems together into a unified resource through a shared informatics infrastructure. Cancer Centers with experience in successfully developing tools in this domain are acting as developers, while other Centers are included as testing and validation sites. Cancer Centers that have expressed an interest in sharing information regarding specimen repositories and data sets are participating as early test sites, providing an opportunity to demonstrate how the tools perform in actual practice.

Translational research. The process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the prevention or treatment of human disease.

Uniform Biological Material Transfer Agreement (UBMTA). A standardized material transfer agreement with generic language for biological material transfers. It was created to increase the efficiency of the process by decreasing delays in research progress during negotiation of material transfer agreements, while providing uniform protection for biological materials. The National Institutes of Health published the Uniform Biological Material Transfer Agreement in 1995 and recommends its use by all public and nonprofit research institutions. The Association of University Technology Managers (AUTM) administers the process of becoming a signatory to the

Master Agreement. See *http://www.autm.net/aboutTT/aboutTT_umbta.cfm.*

Use case. A description of the process used to perform a particular modeling task on a particular model. It is a user-centered description of the activities performed by a user to accomplish a particular goal. The collected use cases specify all the ways the system can be used.

Dated: April 10, 2006.

John Niederhuber,

Deputy Director, Translational and Clinical Sciences.

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BILLING CODE 4140–01–P

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

[USCG–2006–24540]

Privacy Act of 1974; System of Records

AGENCY: United States Coast Guard, Department of Homeland Security.

ACTION: Notice of Privacy Act system of records.

SUMMARY: The United States Coast Guard in the Department of Homeland Security is creating a new system of records for the secure collection of information from and about individuals and entities subject to the requirements of the Maritime Transportation Security Act of 2002.

DATES: The new system of records will be effective May 30, 2006, unless comments are received that result in a contrary determination.

ADDRESSES: You may submit comments identified by docket number USCG–2006–24540 to the Docket Management Facility at the U.S. Department of Transportation. To avoid duplication, please use only one of the following methods:

(1) Web site: *http://dms.dot.gov*.

(2) Mail: Docket Management Facility, U.S. Department of Transportation, Room Plaza 401, 400 Seventh Street, SW., Washington, DC 20590–0001.

(3) Fax: 202–493–2251 (not toll-free).

(4) Delivery: Room PL–401 on the Plaza level of the Nassif Building, 400 Seventh Street, SW., Washington, DC, between 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays. The telephone number is 202–366–9329.

(5) Federal eRulemaking Portal: *http://www.regulations.gov*.

FOR FURTHER INFORMATION CONTACT: Mr. Donald Taylor, U.S. Coast Guard Privacy Officer. Address: Commandant (CG–611), U.S. Coast Guard, 2100 2nd Street, SW., Washington, DC 20593–0001. Telephone number is 202–475–3519.

SUPPLEMENTARY INFORMATION: The Maritime Transportation Security Act (MTSA) of 2002 establishes a comprehensive national system of transportation security enhancements to protect America's maritime community against the threat of terrorism without adversely affecting the flow of commerce through United States ports. The United States Coast Guard (USCG) is the lead Federal agency for maritime homeland security and has significant enforcement responsibilities under the MTSA. Among other responsibilities under the MTSA, the Coast Guard requires that maritime security plans be developed for ports, vessels and facilities, and that those with access to maritime facilities have credentials demonstrating their eligibility for such access.

Homeport, a new system of records under the Privacy Act of 1974, will facilitate implementation of these requirements. Representatives of the maritime industry, members of Area Maritime Security Committees, which are required under the MTSA, other entities regulated by the MTSA, and USCG and other officials will be able to register and use Homeport for secure information dissemination and collaboration. In this aspect regulated entities will be able to use Homeport for electronic submission and approval of required security plans and the Coast Guard will be able to verify compliance with security requirements. Homeport will also be used to collect information from and about individuals for whom background screening will be conducted for purposes of establishing USCG-approved identification credentials for access to maritime facilities, and to inform owners and operators of those maritime facilities of the names of persons who have passed the background screening. Homeport also has the capability to be used as a communications tool in the event of a natural disaster or other emergency to facilitate secure communications.

The Privacy Act embodies fair information principles in a statutory framework governing the means by which the United States Government collects, maintains, uses, and disseminates personally identifiable information. The Privacy Act applies to information that is maintained in a ''system of records.'' A ''system of records'' is a group of any records under the control of an agency from which information is retrieved by the name of the individual or by some identifying number, symbol, or other identifying particular assigned to the individual. Information in Homeport about registered users and those subject to screening for purposes of credentialing will be maintained in a system of records.

The Privacy Act requires each agency to published in the **Federal Register** a description denoting the type and character of each system of records that the agency maintains, and the routine uses that are contained in each system to make agency recordkeeping practices transparent, to notify individuals regarding the uses to which personally identifiable information is put, and to assist the individual to more easily find such files within the agency. Individuals may request their own records that are maintained in a system of records in the possession or under the control of DHS by complying with DHS Privacy Act regulations (6 CFR 5.21).

USCG is hereby publishing the description of the Homeport system of records. In accordance with 5 U.S.C. 552a(r), a report of this new system of records has been provided to the Office of Management and Budget (OMB) and to the Congress.

DHS/CG 060

SYSTEM NAME:

Homeport

SECURITY CLASSIFICATION:

Unclassified, Sensitive.

SYSTEM LOCATION:

The system is located at the United States Coast Guard Operations Systems Center, 600 Coast Guard Drive, Kearneysville, WV 25430–3000.

CATEGORIES OF INDIVIDUALS COVERED BY THE SYSTEM OF RECORDS:

This system of records covers individuals including, but not limited to, representatives of the maritime industry, members of Area Maritime Security Committees, entities regulated under the maritime Transportation Security Act, and government officials. These persons may complete on-line forms and/or request an account to provide the information requested or required by the Coast Guard, access/view sensitive but unclassified information, and participate in collaboration communities. This system will also cover individuals for whom background screening will be conducted for the purpose of establishing Coast Guard-approved identification credentials for access to certain regulated facilities. These individuals include, but are not limited to, facility