

Policy Name: Functions of Biospecimen Repositories	Policy Number: 11.1
Section: Biospecimen Repositories and Translational Research – 11	Date Revised: January 1, 2018

11 Alliance Biorepositories and Biospecimen Resource (ABBR) and Translational Research

11.1 ABBR Infrastructure and Oversight

11.1.1 The Alliance **ABBR** is comprised of five federated biorepository facilities located at four academic medical centers.

11.1.1.1 Alliance Biorepository at the Ohio State University (OSU). Formerly known as the “CALGB PCO”, this facility stores primarily fixed tissue and biofluids from legacy, CALGB solid tumor and lymphoma studies, as well as solid tumor and biofluid biospecimens from newer Alliance studies.

11.1.1.2 Alliance Hematological Malignancy Biorepository (HEME). Formerly known as the “CALGB Leukemia Bank”, this facility also resides at The Ohio State University and stores specimens from patients with acute or chronic leukemia, myelodysplastic syndrome, or multiple myeloma who are enrolled on an Alliance protocol. HEME primarily receives blood and bone marrow specimens, and, in some cases, buccal smears.

11.1.1.3 Alliance Lung Cancer Tissue Bank (LCTB). The Alliance Lung Cancer Tissue Bank (LCTB) is located at the Brigham and Women’s Hospital in Boston, MA. The purpose of the LCTB is to collect, catalog and store frozen samples of lung carcinoma and when possible, portions of involved lymph nodes and adjacent uninvolved lung tissue obtained from previously untreated patients. In addition to tissue specimens, blood samples are also collected pre- and post-resection from the patients to provide a source of quality DNA, RNA and protein for molecular studies.

11.1.1.4 Alliance Biorepository at Washington University in St. Louis (WUSTL). Formerly known as the “ACOSOG Specimen Bank” this CAP-accredited facility collects and stores frozen and fixed tissue, and biofluids from breast, lung, GI, and other solid tumor Alliance trials.

11.1.1.5 Alliance Biorepository at Mayo Clinic (MAYO). Formerly known as the “NCCTG Biospecimen Resource”, this second CAP-accredited facility processes and stores biospecimens associated with neuro-oncology studies, and is also the designated repository

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for processing and storing biospecimens associated with Alliance NCORP studies.

- 11.1.2** Biospecimen tracking, reporting, and inventory management is integrated across all biorepository sites and centrally coordinated at the WUSTL biorepository, through the use of the Alliance BiOMS biospecimen management tool.
- 11.1.3** Although each biorepository site maintains its own local set of policies and standard operating procedures to comply with institutional requirements, those individual site policies specifically pertaining to Alliance trial biospecimen integrity and management are harmonious and meet the minimal standards set forth in this document.
- 11.1.4** The ABBR is supported by a National Cancer Institute (NCI) U24 funding mechanism. Each of the Alliance biorepository leaders at the four academic institutions serve as a co-Principal Investigator (PI) on the U24 grant, with the WUSTL bank director currently serving as contact PI.
- 11.1.5** One or more of the ABBR U24 grant PIs also serves on the Alliance Translational Research Program (TRP) Executive Committee and the Alliance Executive Committee. These appointees are charged with ensuring that the ABBR serves the needs of the NCTN Alliance network.
- 11.1.6** Three of the ABBR U24 grant PIs (or their designees) also serve on the NCTN Group Banking Steering Committee (GBC). The GBC is charged with developing and adopting harmonized policies and practices across all NCTN biospecimen resources.
- 11.1.7** The TRP Executive Committee is primarily responsible for oversight of compliance of the Alliance repositories with Alliance and NCI policies regarding specimen collection and distribution. In addition, this committee is responsible for ensuring that the repositories follow the NCI guidance document “Best Practices for Biospecimen Resources” that was published and updated in 2011. Each Alliance biorepository site will undergo periodic audits to ensure compliance with the NCI Best Practices (<http://biospecimens.cancer.gov/practices>) and oversight for the audits will be a function of the TRP Executive Committee.
- 11.1.8** The Alliance Translational Research Program (TRP), the TRP biorepository sub-committee, study chairs and correlative science co-chairs, individual disease/modality/discipline committees (usually the vice-chair of the

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disease/modality/discipline in charge of translational research) are jointly responsible for: (1) determining biospecimens that should be collected on each Alliance trial and the appropriate methods for collection and processing of those biospecimens and (2) ensuring that the ABBR sites have the appropriate quality control and quality assurance procedures in place for biospecimen handling, processing, storage and distribution.

11.1.9 As the Alliance steward of biospecimens, each biorepository director agrees to procure, store, process and distribute the specimens according to Alliance and NCI policy. In addition, if the biorepository does not comply with Alliance policy, the Alliance can move the biospecimens to another approved Alliance location.

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11.2 Biorepository Functions

The ABBR serves a number of important functions in the context of NCTN Alliance clinical trials. These roles include, but are not limited to:

11.2.1 Biospecimen Collection. The ABBR may design, construct, and distribute supplies and ‘kits’ to facilitate biospecimen collection from remote sites. It is the responsibility of the ABBR to ensure that the design of such materials maintain biospecimen integrity during collection and transport while minimizing cost and logistical complications at the clinical site. The ABBR is also responsible for prospectively tracking and reporting on biospecimen collection activities for all Alliance clinical trials and when necessary, work with other Alliance team members to resolve systematic hindrances with biospecimen collection.

11.2.2 Storage. The ABBR is responsible for storing all biospecimens collected on NCTN and NCORP Alliance trials using methods that optimally preserve biological integrity and ensure biospecimen security.

11.2.3 Processing. The ABBR may be responsible for initial processing of tissue and biofluid specimens to a stable state for long-term storage. This may include centrifugation and/or separation of blood components and processing or embedding of tissue samples. At the discretion of each ABBR biorepository PI, the trial-associated biorepository site may develop and validate specialized processing methods to support specific trial procedures. An ABBR site may also perform secondary processing procedures, such as nucleic acid extraction, tissue sectioning, or tissue microarray (TMA) construction in order to create ‘assay ready’ materials that may be distributed for correlative science studies.

11.2.4 Quality Assurance. The ABBR is responsible for conducting or facilitating the conduct of quality assurance procedures for all collected biospecimens. This includes documenting physical quality of all specimens received, ensuring that proper biospecimen identification is preserved, facilitating histopathology review of tissue specimens when necessary, and ensuring that all material leaving the biorepository is fit for purpose and of suitable quality for all studies planned with those biospecimens.

11.2.5 Regulatory Compliance. The ABBR is the custodian and ‘honest broker’ of all biospecimens collected from patients enrolled on Alliance clinical trials. The ABBR ensures that biospecimens are appropriately de-identified and utilized for scientific studies that are commensurate with the corresponding patient informed consent.

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11.2.6 Distribution. The ABBR works with other components of the Alliance to facilitate the review and distribution of biospecimens for correlative science studies.

11.2.7 Direct submission. For all Alliance trials, the ABBR should be the primary resource for all biospecimen collection, processing, and storage activities. In some cases, however, it may not be desirable or feasible to have biospecimens sent or processed by the ABBR. In these cases, with permission from the Director of Translational Research Operations and/or the Principal Investigator of the Alliance Translational Research Program, biospecimens may be sent directly to an investigator or commercial laboratory. However, even in such cases the investigator or commercial laboratory must follow all policies and procedures related to Alliance biospecimen tracking and handling (as outlined in this document). Furthermore, all biospecimens still remain under the custodianship of the ABBR and any remnant specimens must be returned to the ABBR at the completion of the assay. Examples include:

11.2.7.1 Assay requires rapid processing of fresh biospecimens using a technology or platform that is not available at the ABBR.

11.2.7.2 Assay is consumptive of the entire biospecimen and no material would remain for banking or future use anyway.

11.2.7.3 Assay is an integral biomarker assay that must be performed in a clinically accredited clinical laboratory and/or with rapid turnaround time, following clinical standards of biospecimen identity management and chain of custody.

11.2.8 Depending upon the specific trial design, the ABBR may support biospecimen activities for three different study types as defined by the NCI, the NCTN, and the Alliance. Each activity may be supported by a different funding mechanism, as explained below.

11.2.8.1 Integral Biomarker Studies. Studies in which biospecimens are mandatory and collected to perform an assay (or pathology review) in ‘real-time’ for the purposes of determining patient eligibility, arm assignment, or stratification. As noted above, biospecimens collected for integral biomarker studies may be sent directly to the relevant assay lab. However, once the biomarker assay is complete, unused biospecimens must be sent to the ABBR for other embedded or secondary use studies, unless determined otherwise by the ABBR director.

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11.2.8.2 Integrated (Embedded) Correlative Studies. Studies in which biospecimens are collected to perform a well described, pre-defined correlative biomarker study that may be a secondary or tertiary end point of the trial itself. Collection may or may not be mandatory. With appropriate consent, remnant biospecimens from integrated correlative studies may be stored and used for stand-alone secondary correlative science studies.

11.2.8.3 Biobanking for Stand-alone Secondary Correlative Studies. Collection of biospecimens in the absence of a specific study that is described in the trial protocol itself, but that may be stored and made available for future studies proposed by investigators within or outside of the Alliance or the NCTN groups.

11.2.9 In addition to facilitating biospecimen collection for Alliance clinical trials, the ABBR may serve as a biorepository site for any NCTN intergroup trial, even if the Alliance is not the ‘lead group’ for that trial. As described below, support for intergroup trial biobanking activities must be pre-arranged prior to trial activation.

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11.3 Biospecimen Collection Funding

A number of different funding mechanisms support ABBR activities. Funding is dependent upon the trial and the nature of the activity.

11.3.1 NCI U24 Biorepository Funding. The Alliance U24 biorepository grant is designed to support the staff and resources necessary for basic biorepository operations that include routine biospecimen processing, biospecimen storage, biospecimen information management, and administrative functions. Activities that are NOT supported by U24 funding include:

- 11.3.1.1** Design, manufacturing, and shipping of specialized biospecimen procurement kits.
- 11.3.1.2** Procedures related to biospecimen procurement at the site.
- 11.3.1.3** Biospecimen shipping.
- 11.3.1.4** Specialized biospecimen processing.
- 11.3.1.5** Pathologist time for central pathology review to confirm diagnosis.
- 11.3.1.6** Extraction of nucleic acids, or other secondary biospecimen processing.

11.3.2 Clinical Trial Budget. For some trials where biospecimen collection, processing, or pathology review is integral to the trial itself, these expenses may be primarily part of the trial budget and supplemented by U24 biorepository funding where appropriate. Otherwise, funding may be obtained from other sources noted below.

11.3.3 BIQSFP. The NCI BIQSFP mechanism may be used to support the conduct of integral and/or integrated biomarker studies as well as the expense of biospecimen procurement, shipping, and processing to conduct those studies. This funding mechanism will not support collection of biospecimens for other correlative studies or biobanking purposes.

11.3.4 Non-NCI Funding. Funding from other non-NCI sources (e.g. Komen Foundation, DOD, Breast Cancer Research Foundation), if obtained, may be used to support the construction and distribution of specialized biospecimen collection kits, reimbursement for research biospecimen procurement procedures, and specialized processing at the ABBR, when needed.

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11.3.5 Research Grants (Federal and Non-federal). Investigators requesting biospecimens for either embedded / integrated correlative science studies or secondary use studies should anticipate that there will be nominal costs associated with the preparation (i.e. TMA slides, nucleic acid extraction, tissue quality assurance review) and distribution of biospecimens for funded research projects. These should be supported by research grant budgets, with expenses returned to the appropriate ABBR site to help support operations.

11.3.5.1 Costs for secondary processing of biospecimens for research studies will be charged by each ABBR site. Charges will be dictated by individual ABBR site policies.

11.3.5.2 Additionally, for secondary use studies, a standardized ‘application’ and/or ‘processing fee’ may be charged, in keeping with NCI NCTN policies.

11.3.6 Prior to any trial activation, an appropriate and sufficient funding source(s) should be identified to support all aspects of required biospecimen-related activities, from procurement to distribution. Funding resource(s) for integral biomarker must be secured prior to study activation.

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11.4 Correlative Science and Biospecimen Collection Protocol Development

11.4.1 Proposals to utilize the specimens collected in a prospective trial ideally should be included in the clinical trial protocol concept at the time it is submitted to the Alliance Study Concept Review Committee. An appropriately powered, foreseeably funded, biospecimen-based correlative science study with a strong biological and/or clinical rationale may be included as a secondary end-point of the trial itself and will not need further review or approval once it has been approved in the context of the trial itself.

11.4.2 Once an NCI-approved trial concept moves to protocol development phase, stakeholders from the TRP Pathology Committee and/or TRP Biorepository Committee should begin immediate work with the Alliance Offices, disease/modality/discipline committee, Alliance Statistics and Data Center, Trial study chair(s), and Correlative Science co-chair(s) to develop the integral /integrated / biobanking study plan and biospecimen collection logistics.

11.4.3 Investigators performing laboratory studies may serve as study chairs of Alliance correlative science companion trials.

11.4.4 All embedded correlative science (CS) research requires review and approval by the disease/modality/discipline committee and TRP prior to submission of the main study to the NCI for final protocol approval. Subsequent review of the embedded CS research may be also required by the Alliance biorepository and disease/modality/discipline committee CS vice chairs during the protocol development process. Additional review of other relevant Translational Research Program sub-committees, such as Pathology Committee, Imaging Committee, Pharmacogenomics and Population Pharmacology Committee, Sequencing Committee may also be required for some studies.

11.4.5 Collection time points and biospecimens to be collected at each time point will be defined in a biospecimen collection calendar. Considerations in developing the correlative science and biospecimen collection plan include:

11.4.5.1 Biospecimens that are required for planned integral / integrated biomarker studies.

11.4.5.2 Low cost, minimally invasive collection opportunities (ideally synchronized with collections required for integral / integrated biomarker studies or standard of care) that can be leveraged to create a trial-based biospecimen resource for future correlative science studies.

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- 11.4.5.3** Biospecimens, collection methods, and collection time points that minimize cost and simplify the logistics of collection, shipping, and processing.
- 11.4.6** Protocols that include a “research use only” biopsy must specify eligible biopsy location(s), methods and number of cores must be defined, along with other protocol specific requirements. Source(s) of funding for research tissue collection must be identified (see section 11.3).
- 11.4.7** Protocols that require extensive specimen sampling or processing, non-standard specimen collection time point, or the use of “kits” must be reviewed and approved by the TRP Operation Director and the ABBR director. Source of funding for any “kits” or special collection materials must be identified (see section 11.3).
- 11.4.8** Protocols that require central pathology review require approval by the TRP Operation Director and Pathology Committee. Source(s) of funding for real time central pathology review must be identified (see section 11.3).
- 11.4.9** Protocols that require central imaging review require approval by the TRP Operation Director, Imaging Committee and Imaging and Radiation Oncology Core lab (IROC). Source(s) of funding for real time central pathology review must be identified (see section 11.3).
- 11.4.10** Protocols that require international specimen shipping must be reviewed and approved by the TRP Operation Director and the ABBR director. Sources of funding for international specimen delivery must be identified (see section 11.3).
- 11.4.11** Although not required, it is strongly recommended that the study chair contact the TRP Operation Director, TRP Executive Officer, the ABBR director, and the appropriate disease committee CS co-chairs, the disease pathology cadre leaders, the disease Imaging Committee liaison, or other relevant TRP subcommittees, if applicable, prior to study concept submission to the SCRC.
- 11.4.12** Amendments to the main study wherein the embedded CS research is modified require review and approval by the main Study Chair, Correlative Science Study co-Chair, study statistician, and TRP Operation Director. If these changes involve modification to the standard protocols for biospecimen collection, processing, or shipping, then review and approval is also needed from the ABBR director. If these changes involve modification to the standard protocols

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for imaging collection or processing, then review and approval is needed from the Alliance Imaging Committee and/or IROC.

- 11.4.13** Once a biospecimen collection schedule is created and approved by all stakeholders, a budget will be created. Based upon the cost and the parameters discussed in section 11.3 Biospecimen Collection Funding, appropriate funding must be identified.
- 11.4.14** The ABBR site that will support biospecimen collection for a trial will be determined by the ABBR director, with approval from the corresponding ABBR site director. Considerations for choosing the ABBR site include:
- 11.4.14.1** Existing site capacity and resources to manage a new collection.
 - 11.4.14.2** Need for central pathology review or other correlative science support. To minimize shipping costs and logistical complications, trials where pathology support or correlative study assays will be provided by an institution that is also an ABBR site should also use that site for biobanking.
 - 11.4.14.3** Biospecimens from neuro-oncology and Alliance cancer control program trials will be preferentially banked at the MAYO site.
 - 11.4.14.4** Biospecimens from hematological malignancy trials will be preferentially banked at the HEME site.
- 11.4.15** Sites with logistical inability (e.g., sites outside the continental U.S.) to collect, process and ship specimens according to the protocol must apply for a waiver for exemption with the Alliance Protocol Operations Office, the Alliance TRP, the Alliance Statistics and Data Center (SDC), the study chair and the disease/modality/discipline committees. An administrative memorandum stating the shipping issue(s) and any protocol violation(s) from the site must be approved and filed with Protocol Operations through the assigned Protocol Coordinator prior to study activation. Collection, processing and shipping instructions for these sites will be provided on a study-by-study basis by the assigned biorepository.

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11.5 Biospecimen Collection Policies

- 11.5.1** Each trial protocol document or associated Correlative Science Manual (CSM) must specify how to collect, prepare and ship specimens to the appropriate ABBR site. Questions regarding the collection and/or shipment of the materials should be directed to the assigned biorepository site where the specimen is being sent.
- 11.5.2** Each trial protocol or CSM document will follow a standard set of protocols (SOPs) for biospecimen collection, shipping, and processing.
- 11.5.3** All sites are required to send protocol-mandated biospecimens to the appropriate ABBR site, providing that appropriate patient consent is obtained and it is physically possible to send such biospecimens.
- 11.5.4** In cases where institutional policy prohibits the release of clinical pathology tissue blocks, an enrolling site may receive permission to submit a tissue block alternative (such as unstained slides or a tissue punch from the block) provided that permission is granted by the TRP Operations Director and trial study chair(s) and study co-chair(s). Note that for some protocols, submission of a tissue block may be absolutely required for participant enrollment.
- 11.5.5** ABBR biorepository sites themselves are not clinically-accredited medical laboratories. Therefore, any biospecimen processing that must be performed by a clinically accredited analytical laboratory (e.g. for integral biomarker testing or return of individual patient results) should not be performed by the Alliance biorepository. The Alliance biorepository is allowed to receive and store slides for retrospective histopathology review. All local diagnostic slides submitted for histopathology review can be returned to submitting sites upon request.
- 11.5.6** All specimens shipped to Alliance repositories must have patient consent and be accompanied by the appropriate paperwork as outlined in the protocol (e.g. forms, pathology report, etc.).

Policy Name: Biospecimen Processing and Storage Policies	Policy Number: 11.6
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11.6 Biospecimen Processing and Storage Policies

- 11.6.1** For diagnostic clinical pathology tissue specimens that have been submitted to any Alliance repository, the appropriate representative sections and/or cores will be prepared and the block will remain on file and will be available to the submitting institution for any medical-legal need.

Policy Name: Biospecimen Reporting and Tracking	Policy Number: 11.7
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11.7 Biospecimen Reporting and Tracking

- 11.7.1** All biospecimens submitted by sites are tracked by a database system (the Biospecimen Management System—BIOMS). Any exception must be granted by the ABBR director.
- 11.7.2** Each specimen submitted must be accompanied by the appropriate paperwork, as required by the protocol. Local records are kept in addition to the database. Local records will be secured in a locked cabinet/office at all times and database security will follow that recommended by the Alliance Statistics and Data Center (SDC).

Policy Name: Patient Consent, Confidentiality, and Regulatory Compliance	Policy Number: 11.8
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11.8 Patient Consent, Confidentiality, and Regulatory Compliance

11.8.1 Patient consent for studies must be obtained prospectively. Consent forms must include adequate information to assess risks.

11.8.2 For trials that involve integral biomarker assessment to determine eligibility or treatment stratification, biospecimen submission for the integral biomarker assay is mandatory from all sites and all patients. All non-integral embedded correlative science requiring specimen submission must be offered to all patients enrolled on the study, although patients may opt not to participate. Therefore, specimen submission for non-integral correlatives, in general, is optional for the patient but not optional for the site. Exceptions to site participation in specific embedded correlative science studies may be granted by the study chair(s), in consultation with the corresponding correlative sciences co-chair(s) and the Translational Research Program Principle Investigator, in circumstances when the requisite resources or other infrastructure are not available at that site. In some rare instances, non-integral specimens can be mandatory for patients to participate after the group chair and/or the principal investigator of the Translational Research Program grant permission.

11.8.3 In the case of future (secondary use) studies that will use biospecimens collected for an Alliance clinical trial, including germ line susceptibility studies (studies of heritable genes), participants are asked to grant broad permission (i.e., it is unknown exactly what tests might be appropriate or performed in the future at the time the specimen is banked). Participants will NOT be re-contacted for each individual study.

11.8.4 Previously banked material that was not originally intended for extensive DNA studies (e.g., whole genome sequencing, whole exome sequencing, and genome-wide association studies) and for which informed consent was not originally obtained may be used for such research, but in these cases whether a re-consent must be obtained from the participant at the institutional level or not will be determined by the Alliance Ethics committee. For deceased patients, where re-consent is not practicable, whether a waiver of consent must be obtained at the institutional level or not will also be determined by the Alliance Ethics committee.

11.8.5 A unique Alliance biospecimen identification number will be assigned to each biospecimen submitted to Alliance Biorepositories. At the Alliance biorepositories, biospecimens must be stored and distributed with this number only. Investigators may not receive any patient identifiers, only the unique

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biorepository specimen number. However, this may not apply to biospecimens sent directly to an investigator or commercial laboratory (see section 11.2.7).

- 11.8.6** Only authorized biorepository personnel may have access to match the unique sample ID with the Alliance patient ID number and only authorized Alliance statisticians may have the ability to link the unique specimen ID number, patient information, and clinical outcome. Exceptions must be approved by the principal investigator of the Translational Research Program and the group statistician for the Alliance.
- 11.8.7** If a registered patient withdraws consent from treatment but agrees to be followed on protocol, biospecimens may be submitted as required by the protocol.
- 11.8.8** If a registered patient withdraws consent for participation in the study or consent for follow-up, biospecimens may not be submitted.
- 11.8.9** If biospecimens have already been submitted but not distributed to investigators at the time when the patient withdraws consent, those biospecimens will be withdrawn from the repository and will be disposed of appropriately – either destroyed or, in the case of tissues, returned to the submitting institution upon request. Attempts will be made to retrieve any specimens that have been sent from the repository to investigators. However, processed specimens and the research data generated from them will not be rescinded, and may be used in study analyses.
- 11.8.10** Biospecimens are not released from the repository to investigators until the Alliance statistician assigned to the study or designee confirms the record of patient consent in the Alliance database. If a specimen is present in the repository but is later found to not have the appropriate patient consent, the specimen will be withdrawn from the repository and will be disposed of appropriately – either destroyed or, in the case of a diagnostic clinical pathology tissue blocks, returned to the submitting institution.
- 11.8.11** It is the Alliance policy that the Alliance biorepository shall not release clinical, pathology reports submitted by sites to correlative science investigators. Requests for data elements collected from local pathology reports should be submitted to the Alliance Data Center. This rule does not apply to study pathologists performing retrospective central reviews.

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- 11.8.12** Disagreement between investigators and statisticians with respect to consent language for specific analyses will be adjudicated and decided by Alliance ethics leadership, statisticians, and the translational research program.
- 11.8.13** Reports (including manuscripts, abstracts, and progress reports) may never list any patient by name or initials. If needed, only unique identification codes may be used.
- 11.8.14** Unless indicated in the protocol and performed in a CLIA-certified laboratory, results from correlative science studies may not be provided to the patient or physician. Upon request, information may be made available as aggregate data in the form of abstracts or manuscripts.
- 11.8.15** The Alliance maintains Certificates of Confidentiality for each of its repositories from the US Department of Health and Human Services (HHS), which protects against the involuntary release of information collected during the course of the study. The researchers involved in a project may not be forced to identify a patient in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the HSS, or for purposes of program review or audit.
- 11.8.16** For biospecimens sent directly to an investigator or commercial laboratory, certain Protected Health Information (PHI), such as patient initials and collection dates, may be sent to the investigator/commercial laboratory along with the biospecimens. In those cases, the trial protocol and informed patient consent form will inform sites and patients of any potential regulatory considerations.

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11.9 Biospecimen Pathology Review

11.9.1 In no cases will the Alliance or an Alliance study pathologist render a clinical diagnosis. It is assumed that the submitting institution and the appropriate institutional pathologist will have rendered a clinical diagnosis in a way that is most appropriate for standard of care for the patient, prior to submission. In particular, fresh, ‘research only’ biopsy specimens will not receive a clinical diagnosis from an Alliance pathologist. If it is deemed necessary to make a histopathologic diagnosis of a biospecimen collected from a patient with an uncertain diagnosis (e.g., a metastatic lesion of a presumptive but unconfirmed primary origin), then it is incumbent upon the institution to perform any necessary diagnostic evaluation prior to submitting the biospecimen to the Alliance, even if the trial will perform a central pathology review.

11.9.2 In any case involving an apparent significant discrepancy between an observation made by an Alliance study pathologist and a diagnosis rendered at the submitting institution, the Alliance pathologist takes the following steps to determine the nature of the problem:

11.9.2.1 The study pathologist will verify the case identifiers. If the case was submitted to the Alliance biorepository for retrospective central diagnosis confirmation, the study pathologist will notify the biospecimen repository regarding the potential diagnostic discrepancy in the case. If the problem is clerical (e.g., incorrect specimen submitted to or distributed from the biorepository), the study pathologist and/or repository rectifies the problem directly with the submitting institution through Alliance institutional personnel (e.g., the institutional clinical research professional).

11.9.2.2 If it is determined that all case identifiers are correct, the Alliance study pathologist will contact the institutional clinical research professional (CRP) and, if necessary, will arrange to contact the submitting pathologist. The Alliance study pathologist will discuss the case with the submitting pathologist and detail the findings and the need for a re-review by the submitting institution. The Alliance study pathologist will discuss with the responsible institutional CRP and/or submitting pathologist whether other/additional pathologic materials from that case exist that might explain a discrepancy. Any problems related to case identification, specimen selection, or additional diagnostic information or materials will be discussed and resolved, if possible, by this direct communication,

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and the nature of the resolution will be communicated to the repository by the study pathologist.

11.9.2.3 If an apparent discrepancy still exists, the appropriate Pathology Committee leader and at least one other committee member will review the case to confirm the diagnostic discrepancy. It is highly recommended that the study pathologist, the pathology committee leader and the submitting pathologist discuss the case directly before the final confirmation of discrepancy.

11.9.2.4 If the discrepancy is confirmed, the study pathologist or the chair of the Pathology Committee will immediately report the correct diagnosis to the responsible data coordinator. The data coordinator will report the correct diagnosis to the clinical research professional at the submitting institution. It is the responsibility of the clinical research professional to notify the submitting pathologist and the physician who registered the patient that there is a difference in diagnosis. The Alliance SDC will consider the discrepancy in the final analysis of the study.

Policy Name: Accessing Banked Biospecimens Overview	Policy Number: 11.10
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11.10 Accessing Banked Biospecimens Overview

- 11.10.1** An Alliance membership is not required to request Alliance specimens.
- 11.10.2** Samples are furnished to the investigator by the appropriate Alliance specimen repository for the purpose of the project as approved. Research must be limited to that described in the approved protocol. Investigators may not share any portion of specimen or derivative specimen with another investigator or lab without permission of the NCI and the Alliance.
- 11.10.3** Investigators must discuss return of all unused specimens to the Alliance specimen repository prior to the completion of their correlative study. This includes RNA, DNA, urine, plasma, serum, tissue, slides, unstained sections, etc.
- 11.10.4** When investigators request specimens for nucleic-acid based (RNA / DNA) studies, it is the policy of the ABBR that whenever possible, only nucleic acid derivatives aliquots prepared by the ABBR will be distributed to the investigators. Exceptions can only be made with approval from the ABBR director.
- 11.10.5** No diagnostic, clinical pathology tissue blocks shall be released to research investigators. In general, no research blocks shall be released to research investigators either. However, exceptions for research block release may be granted by the ABBR director.
- 11.10.6** Once the project is approved, the investigator will be responsible for ensuring that his/her research is conducted under regulatory policies (human subjects, intellectual property, material transfer) governing their individual institution, as well as those set forth by the Alliance/NCI.
- 11.10.7** Correlative science investigators are required to have funding for their projects prior to receiving specimens.
- 11.10.7.1** In order to facilitate the successful application for funding, the Alliance will review concepts without established funding. For this review, investigators must provide the information requested for a preliminary concept review. In order to receive a letter of support from the Alliance, interested investigators must provide a preliminary concept at least six weeks prior to the grant deadline. Exceptions to this rule have to be approved by the principal investigator of the Translational Research Program.

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11.10.7.2 Approved preliminary concepts, must include a description of the collaboration with the Alliance in their proposal submission and they must comply with the Alliance guidelines, which have been written to ensure scientific integrity, patient confidentiality, specimen protection, and support of the Alliance infrastructure resources.

11.10.7.3 Any collaboration with the Alliance that impacts Alliance resources, including protocol development, data management, statistical analysis, and specimen banking may require additional funding support. In addition to funds to support laboratory science (supplies, equipment, personnel, etc.), investigators may also be required to establish contracts and agreements with the Alliance, and/or subcontracts with the different resource offices of the Alliance being used, including the following:

11.10.7.3.1 Alliance Group Chair’s Office

11.10.7.3.2 Statistics and Data Center (for data management and statistical support)

11.10.7.3.3 Any relevant biorepository (for sample preparation and distribution, etc.)

11.10.8 Subcontract arrangements must be performed in accordance with Alliance policy and submitted in advance to ensure appropriate time is given for review and sign-off. A final copy of the grant must be submitted to and approved by the Alliance before submission to the granting agency.

Policy Name: Stand-alone Secondary Biospecimen Use Studies	Policy Number: 11.11
Section: Biospecimen Repositories and Translational Research – 11	Date Revised: January 1, 2018

11.11 Stand-alone Secondary Biospecimen Use Studies

- 11.11.1** Any proposal to utilize biospecimens from an Alliance NCTN study will be reviewed by the NCI NCTN Core Correlative Science Committee (CCSC) through a process managed by NCI. NCI NCTN-CCSC is charged with scientific review & prioritization of proposals requesting use of banked, non-reserved biospecimens collected from NCTN trials for use in correlative science studies. NCTN-CCSC prioritization ensures optimal use of these irreplaceable clinical trial biospecimens.
- 11.11.2** All correlative science investigators must agree to use the specimens for only the NCI NCTN-CCSC-approved research project and to follow Alliance and NCI policies and procedures. Investigators will be charged for all services that the biorepository provides (see 11.3)
- 11.11.3** Submission to the Alliance Translational Research Program for approval is strongly encouraged, but not required to obtain specimens from Alliance NCTN studies. A letter of support will be provided for the proposals endorsed by the Alliance.
- 11.11.4** A correlative science proposal should be based on an innovative idea, built around a strong biologic hypothesis including preliminary data supporting the hypotheses and/or feasibility, be scientifically valid and have significant clinical relevance. The investigator must demonstrate expertise, both technical and scientific, relevant to the work proposed. Therefore, previous publications in the area and/or preliminary data are required. Preliminary data are also required to evaluate the scientific rationale and logistics of the concept, the performance characteristics of the assay(s) to be employed (including accuracy compared to a gold standard, reproducibility, variability, and/or other available analytic validation), and to demonstrate clinical relevance.

Policy Name: Data Generation, Ownership, and Publications	Policy Number: 11.12
Section: Biospecimen Repositories and Translational Research – 11	Date Revised: January 1, 2018

11.12 Data Generation, Ownership, and Publications

- 11.12.1** Data from all laboratory tests performed on samples from any Alliance repository will be submitted to the Alliance SDC, usually via electronic means. The analysis of the data will be conducted by the responsible Alliance statistician or designee with the necessary expertise. The designee must be approved by the principal investigator of the TRP and the group statistician. The group statistician must approve any exception to this rule.
- 11.12.2** All publications must be reviewed and approved by the Alliance, following guidelines in the Alliance Policies and Procedures. The grant support of the appropriate Alliance repository will be acknowledged in publications.