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Biospecimen Reporting for Improved Study Quality (BRISQ)

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Abstract

Human biospecimens are subject to a number of different collection, processing, and storage factors that can significantly alter their molecular composition and consistency. These biospecimen preanalytical factors, in turn, influence experimental outcomes and the ability to reproduce scientific results. Currently, the extent and type of information specific to the biospecimen preanalytical conditions reported in scientific publications and regulatory submissions varies widely. To improve the quality of research utilizing human tissues it is critical that information regarding the handling of biospecimens be reported in a thorough, accurate, and standardized manner. The Biospecimen Reporting for Improved Study Quality (BRISQ) recommendations outlined herein are intended to apply to any study in which human biospecimens are used. The purpose of reporting these details is to supply others, from researchers to regulators, with more consistent and standardized information to better evaluate, interpret, compare, and reproduce the experimental results. The BRISQ guidelines are proposed as an important and timely resource tool to strengthen communication and publications around biospecimen-related research and help reassure patient contributors and the advocacy community that the contributions are valued and respected.

Introduction

Human biospecimens provide the basis for research leading to better understanding of human disease and biology, and discovery of new diagnostics and treatments that are tailored to individual patients with cancer or other diseases. These biological materials are subject to a number of different collection, processing, and storage factors that can significantly alter their molecular composition and consistency. Such preanalytical factors can, in turn, influence experimental outcomes and the ability to reproduce scientific results. A growing number of studies have demonstrated the effects of biospecimen preanalytical factors on molecular measurements.[1–7] In biomarker studies, such variations can result in artifacts being misinterpreted as experimental results.[6,8] Preanalytical factors can also contribute to false-negative and false-positive results in assays for determining appropriate therapies for cancer patients.[9,10] Currently, the extent and type of information specific to the biospecimen preanalytical conditions reported in scientific publications and regulatory submissions varies widely. To improve the quality of research using human specimens it is critical that information regarding the handling of biospecimens be reported in a thorough, accurate, and standardized manner.

The purpose of this paper is to make recommendations for the reporting of data elements for human biospecimens, defined as solid tissues and bodily fluids, used in biomedical studies. Cell lines and biospecimen derivatives such as nucleic acids or proteins, while crucial for biomedical research, are not intended to fall within the scope of these recommendations. The Biospecimen Reporting for Improved Study Quality (BRISQ) recommendations are intended to apply to any study in which human biospecimens are used. This includes biomedical applications such as translational science, biomarker discovery, clinical trials, technology development, and diagnostic-assay and therapeutics development. The recommended data elements would be reported by an author in a journal publication, by a company in a regulatory submission, or by a biorepository distributing biospecimens. It is intended that the list and the elements within it will be interpreted, modified, and applied

according to the context of the study being reported. It is also recognized that information corresponding to all data elements may not be available but at least for some categories (described below) the known or unknown status of these elements should be documented.

The list of data elements discussed includes general information for consistent documentation of classes of biospecimens and factors that might influence the integrity, quality, and/or molecular composition of biospecimens. Reporting the details enumerated in the BRISQ list does not guarantee biospecimen quality, and should not be seen as a substitute for empirical quality evaluations. The purpose of reporting these details is to supply others, from researchers to regulatory agencies, with more consistent and standardized information to better evaluate, interpret, compare, and reproduce the experimental results. To maintain consistency with federal regulations on research involving human subjects, information that might enable individual identification of research participants should be withheld.

The BRISQ list has been constructed as an initial step towards defining reporting recommendations. The list will likely evolve as more is learned about the factors that influence biospecimen quality and composition, and in turn their effects on biospecimen analysis. It is envisioned that future iterations of the BRISQ recommendations might include changes to the list of elements and the relative weight thereof in accordance with evidence-based scientific and medical findings and technological developments.

Materials and Methods

A half-day workshop, *Development of Biospecimen Reporting Criteria for Publications*, was held at the National Cancer Institute (NCI) 2009 Biospecimen Research Network Symposium (http://biospecimens.cancer.gov/meeting/brnsymposium) to initiate a discussion on biospecimen reporting recommendations. Workshop attendees included individuals covering a broad range of expertise: laboratory scientists, clinicians, pathologists, statisticians, patient advocates, biobankers, journal editors, leaders of relevant professional societies, and other stakeholders. The attendees noted that reporting guidelines covering many aspects of biomedical studies already exist, particularly guidelines relevant to experimental design and data reporting.[1] It was proposed that the BRISQ recommendations apply to all studies utilizing human biospecimens, and thus complement existing guidelines by filling a niche concerning reporting of biospecimen characteristics and preanalytical variables.

The attendees further proposed that the BRISQ recommendations should broadly encompass solid tissues and bodily fluids, rather than including separate lists for these biospecimen types. It was also agreed that a committee to develop biospecimen reporting recommendations should be formed to take the effort forward. Many of the individuals and disciplines participating in the workshop were included when the BRISQ committee was subsequently formed.

Formulation of the recommendations was based on consideration of what biospecimen information could enable a science reviewer to fully evaluate or replicate a reported study. The preliminary list included the most commonly available data elements. The committee considered the characteristics of the biospecimens themselves as well as numerous preanalytical factors. Types of data elements include the tissue type and the pathology of the sample; patient characteristics that might influence the biospecimens, such as vital and

[1]The EQUATOR project (http://www.equator-network.org/) provides an extensive listing of guidelines for health research.

disease states; and the collection and handling of the biospecimens, e.g., the stabilization, shipping, and storage conditions.

The preliminary list of recommendations was refined by consulting the NCI Biospecimen Research Database (http://brd.nci.nih.gov), an online resource compiling peer-reviewed articles that address biospecimen science. The Biospecimen Research Database's terminology for scientific literature curation that was deemed relevant was incorporated into the initial BRISQ list. This terminology served as a starting point for discussion at monthly teleconferences by the BRISQ committee.

Results

The committee composed a list of data elements that represent factors believed to often influence biospecimen quality and thus should be considered for reporting, *if known or applicable*, for the particular study; for example, some list elements will be more applicable to biospecimens collected for a disease specific study than those collected for a population based biospecimen resource. For clarity, these elements are organized according to the lifecycle of the biospecimen (Figure 1), which spans the period immediately prior to removal from the patient through use in a scientific analysis.

Many reporting elements were discussed, but only some were approved by consensus for inclusion in the guidelines. The committee was mindful that certain information, while important to report, may not have direct relevance to the biology or condition of the biospecimen, and therefore, would not be under the purview of the BRISQ recommendations. The committee attempted to carefully balance scientific interest in having access to extensive data about biospecimen collection, processing, and storage against practical challenges in obtaining such detailed information. Each reporting element included in the guidelines is backed by evidence that the factor could have an effect on the structural integrity and molecular characteristics of the biospecimen or on the ability to perform certain assays on the biospecimen and obtain reliable results. While the committee recognizes that collection of data about biospecimens can increase the operational costs to collect and use biospecimens, cost was not factored into the exclusion of data elements that were or should be considered necessary.

The elements in the BRISQ list are prioritized into three tiers according to the relative importance of their being reported. The first tier, ***items recommended to report***, includes information such as the organ(s) or the anatomical site from which the biospecimens were derived and the manner in which the biospecimens were collected, stabilized, and preserved; for quick reference, these items are summarized in Table 1. Reporting these items need not be onerous. For example, Beatty et al.[11] include most BRISQ Tier 1 items in the following excerpts:

- "FNA [fine-needle aspiration] specimens were obtained from 55 surgically removed specimens of breast cancer within 1 hour of resection, before tissue fixation. The aspirates were obtained using a 22- to 25-gauge needle and spread directly on slides and fixed in ethanol or formalin or placed in CytoLyt for preparation of ThinPrep slides according to the manufacturer's protocol. Corresponding FFPE [formalin-fixed, paraffin-embedded] tissue specimens were fixed in 10% neutral buffered formalin for 18 to 24 hours according to routine procedures and embedded in paraffin."
- "All FNA cytologic slides were air dried and stored at room temperature before FISH analysis."

Items beneficial to report form the second tier. These are data elements an evaluator might find helpful to know but may be slightly less crucial to the scientific contribution or less likely to be annotated, such as the time from biospecimen excision/acquisition to stabilization. ***Additional items to report*** compose the third tier. These include information about conditions that might be useful to know concerning the biospecimens but are not known to be as likely to influence research results or are unlikely to be available to researchers, such as environmental factors to which patients were exposed or the type of storage container in which the biospecimens were kept.

The full BRISQ list featured in Table 2 includes each item and its definition along with additional columns that were designed for an author or reviewer to track where the listed items are reported for a particular study. To the right of the Item Descriptions is a column assigning each item a unique Roman-numeral/letter/number identification code. The far right column provides space to note where each item may be found in a manuscript or application. The far left Apply-to column indicates whether the BRISQ item is applicable to *All* biospecimen types or is more appropriate for solid *Tissue* biospecimens or *Fluid* biospecimens (such as blood, urine, or other fluids). For example, item III.b, “Type of long-term preservation,” is pertinent to all types of biospecimens; item III.b.2, “Time in fixative/preservative solution,” is more relevant to solid tissue than to fluid biospecimens; and item III.c, “Aliquot volume,” applies more often to fluid than to solid tissue biospecimens.

When reporting elements of the BRISQ list, standard operating procedures specifying many of the pertinent details, such as blood-collection protocols, may be provided or referenced; any referenced documents should be publicly available. It is preferable that most Tier 1 items relevant to the biospecimen and particular scientific study be reported directly in the intended publication rather than be cited from another document. Detailed descriptions that are too lengthy to be accommodated should be made available as supplemental materials online. Whether the laboratory performing the study was operating under any formal certification or accreditation should be stated if applicable to the study being reported.

The BRISQ committee discussed whether to request information that the biorepository and/or researcher had obtained ethical clearance to collect the biospecimens and perform the study. Clearance from an institutional review board or similar body is important to report in publications, and its reporting is generally required by journals. However, it is not immediately pertinent to the structural integrity and molecular characteristics of the biospecimen and, thus, is not included in the BRISQ recommendations. Similarly, accurate biospecimen-tracking mechanisms are essential to biobanking but not immediately pertinent to the condition of the biospecimen, and thus are also not included in the BRISQ data-elements list.

Surgical parameters, such as type of anesthesia or receipt of blood or other intra-operative infusates, were recognized to be of potential significance to the condition of the biospecimens. However, these data often are not known. When it is available, information about anesthesia and intraoperative treatments that may influence the condition of the biospecimens should be reported. These elements were not included in the BRISQ list because currently such information is rarely available or not required to be recorded as part of biospecimen collection efforts. If or when surgical parameters are determined to be critical through systematic biospecimen research studies these elements will be integrated into future recommendations.

Several preservation parameters known to influence the condition of biospecimens and the results of analyses have been included in the list of recommendations. Researchers should state the rationale for the chosen preservation parameters. For example, if the type and

temperature of the biospecimen preservative were selected to optimize stability, extraction, and analysis of a particular analyte, this should be mentioned.

The BRISQ committee recognized the need for greater specificity in the anatomic and histologic details reported concerning solid tissue biospecimens. The committee agreed that the level of detail with which pathology characteristics are reported should be enough to sufficiently address the scientific research question. These characteristics include not only the tissue site of the biospecimen and the relation of the biospecimen to the pertinent clinical diagnosis within the tissue site, but also the composition and pathology within the biospecimen where relevant.

The BRISQ committee included members of the NCI Office of Biorepositories and Biospecimen research (OBBR), participants from the OBBR Biospecimen Research Network Symposium, and members of the International Society for Biological and Environmental Repositories (ISBER) and the committees responsible for the REporting recommendations for tumor MARKer prognostic studies (REMARK)[12] and STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)[13] guidelines. Essential harmonization with similar efforts underway by these groups is ongoing.

Discussion

An adage in the business community states, “That which is measured improves. That which is measured and reported improves exponentially.” The BRISQ reporting recommendations represent the product of extensive discussion and input from researchers with varied types of expertise and from many stakeholders, all of whom share the common goal of improving biospecimen reporting and, by extension, fields in which biospecimens are employed. The committee believes that by providing details concerning preanalytical factors that might affect assay results, investigators will further improve the quality of biomedical studies, including research for developing cancer biomarkers for screening, early detection, and treatment.

Adoption of the BRISQ recommendations is expected to help authors, reviewers, editors, and regulatory officials evaluate whether sufficient information about the biospecimens has been provided to enable assessment of the influence of preanalytical biospecimen factors on study results. If reported, this information will allow improved evaluation, interpretation, comparison, and reproduction of the results from studies that employ human biospecimens. Although items in any Tier might not be available or in Tiers 2 or 3 might not be considered significant to report, increased awareness of their potential influence on biospecimen studies might lead to improved tracking and reporting in the future.

The BRISQ recommendations may be implemented by anyone reporting on studies involving biospecimens. Reviewers, editors, and regulatory officials might also employ the list as a tool for evaluating whether sufficient biospecimen information has been included in a manuscript or application. In addition, the recommendations might be employed by investigators requesting biospecimens from a biospecimen resource: essential items on the list might be checked off to indicate the annotation needed for the requested batch of samples. Elements of BRISQ that document preanalytical variables for tissue biospecimens could be economically captured using a reporting system such as the Standard PREanalytical Code, or SPREC, which was recently published by the ISBER Working Group on Biospecimen Science.[14]

BRISQ reporting items will not necessarily be applicable to every study, and authors and reviewers are urged to use their judgment to decide which factors are essential. It is not always possible for investigators to ascertain every recommended element for every

biospecimen, even for Tier 1 items, but unknown elements relevant to the study being reported should be fully acknowledged with a discussion of possible implications that the missing information might have on the study conclusions. Unknown or unreported Tier 1 data elements should not be considered a reason for automatic dismissal of a report or conditional for the award of a grant. The final decision on acceptability of missing Tier 1 information should be specific to the study context.

When consulting the BRISQ list, researchers should evaluate the importance of each item in the context of the study, and adjust their reporting accordingly. An item such as “method of enrichment for relevant components,” listed here as Tier 2 might—for example, in the context of a study comparing the efficacy of various enrichment methods—be essential to report and should thus be considered Tier 1 for that study. The converse may also be true, when, for example, an item listed here as Tier 2—such as “temperature between acquisition and stabilization”—is less pertinent to the study at hand—perhaps because the time at this temperature was negligible—and should be considered Tier 3.

It is hoped that consideration of the BRISQ recommendations will sensitize the biobanking and research communities and their funding agencies to the importance of tracking preanalytical variables, leading to more judicious selection and handling of experimental human specimens and thus improved study quality. Anecdotally, recommendations such as REMARK seem to have had the effect of spurring researchers to consider the recommendations in advance of conducting their investigations, with the result that researchers might take greater care in the design, conduct, and analysis of their studies. The BRISQ committee envisions a similar trajectory for preanalytical biospecimen data elements. Thus, not only might overall quality of publications improve, but the quality of human-biospecimen-dependent investigation in general might improve over time with the formation and adoption of publication recommendations. It is anticipated that biospecimen resources might use these recommendations to improve on their existing standard operating procedures and annotation thereof. Such improvements could include the acquisition of additional relevant biospecimen data based on the BRISQ recommendations and the release of all such data to researchers as a standard procedure. In this way, biospecimen resources might become major players in the universal application of these recommendations.

Patient contribution of biospecimens for research is a voluntary, generous action aimed at helping advance scientific discovery and progress. The research team, pathologist, and biorepository systems, as the stewards of these biospecimens, have a responsibility to be vigilant and persistent in using methods and practices that protect and preserve the highest possible quality biospecimen and associated data. The BRISQ guidelines are proposed as an important and timely resource tool to strengthen communication and publications around biospecimen-related research and help reassure patient contributors and the advocacy community that the contributions are valued and respected. Researchers are further encouraged to strengthen public outreach and education around the use and potential of human biospecimens[15] and the biorepository community as these are emerging and potentially misunderstood areas.

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Figure 1.
The Lifecycle of the Biospecimen.
The preanalytical phase of the lifecycle of the biospecimen includes each stage from Patient to Distribution. Preanalytical variables are addressed in the BRISQ list.

Table 1

Quick-reference BRISQ Summary/Checklist: Tier 1 items to report if known and applicable.

	Data Elements	Examples
❒	**Biospecimen type**	Serum, Urine
	Solid tissue, whole blood, or another product derived from a human being	
❒	**Anatomical site**	Liver, Antecubital area of the arm
	Organ of origin or site of blood draw	
❒	**Disease status of patients**	Diabetic, Healthy control
	Controls or individuals with the disease of interest	
❒	**Clinical characteristics of patients**	Pre-menopausal breast cancer patients
	Available medical information known or believed to be pertinent to the condition of the biospecimens	
❒	**Vital State of patients**	Postmortem
	Alive or deceased patient when biospecimens were obtained	
❒	**Clinical diagnosis of patients**	Breast cancer
	Patient clinical diagnoses (determined by medical history, physical examination, and analyses of the biospecimen) pertinent to the study	
❒	**Pathology diagnosis**	Her2-negative intraductal carcinoma
	Patient pathology diagnoses (determined by macro and/or microscopic evaluation of the biospecimen at the time of diagnosis and/or prior to research use) pertinent to the study	
❒	**Collection mechanism**	Fine needle aspiration, Pre-operative blood draw
	How the biospecimens were obtained	
❒	**Type of stabilization**	Heparin, On ice
	The initial process by which biospecimens were stabilized during collection	
❒	**Type of long-term preservation**	Formalin fixation, freezing
	The process by which the biospecimens were sustained after collection	
❒	**Constitution of preservative**	10% neutral-buffered formalin, 10 USP Heparin Units/mL
	The make-up of any formulation used to maintain the biospecimens in a non-reactive state	
❒	**Storage temperature**	−80 °C, 20 to 25 °C
	The temperature or range thereof at which the biospecimens were kept until distribution/analysis.	
❒	**Storage duration**	8 days, 5 to 7 years
	The time or range thereof between biospecimen acquisition and distribution or analysis.	
❒	**Shipping temperature**	−170 °C to −190 °C
	The temperature or range thereof at which biospecimens were kept during shipment or relocation.	
❒	**Composition assessment & selection**	Minimum 80% tumour nuclei & maximum 50% necrosis
	Parameters used to choose biospecimens for the study	

Table 2

BRISQ table with example references, when available, that exemplify each data element's influence on experimental results. This is not intended to be an exhaustive list.

I. Pre-acquisition				
Apply to	Tier #	Item Description	Item #	Example
All	Tier 1	**Biospecimen type. Solid tissue, whole blood, serum/plasma, isolated cells, urine, secretions, or another product derived from a human being.**	I.a.	16 – 18
All	Tier 1	**Anatomical or collection site. In standard terminology, organ(s) of origin or site of blood draw.**	I.a.1.	29 - 22
All	Tier 1	**Biospecimen disease status. From controls or individuals with the disease of interest; in the case of solid tissue, whether it is from disease site or normal adjacent (not involved but from the same anatomical site as a disease specimen in the same patient).**	I.a.2.	23
All	Tier 1	**Clinical characteristics of patients. In standard terminology, available medical information known or believed to be pertinent to the condition of the biospecimens.**	I.b.	24
All	Tier 1	**Vital state. Alive or deceased when biospecimens were obtained**	I.b.1	25, 26
All	Tier 3	*Disease state. Patient condition relative to disease and treatment, if known (e.g. during- or post-therapy; acute, chronic, or terminal stage).*	I.b.1.1.	27
All	Tier 3	*Cause of death. For postmortem biospecimens, the cause of death and other diseases present at the time of death.*	I.b.1.2.	28 – 30
All	Tier 3	*Agonal state. The patients' physical condition immediately preceding death (e.g. prolonged degeneration or relatively healthy)*	I.b.1.3.	28 – 30
All	Tier 1	**Diagnosis. Patient diagnoses pertinent to the study being conducted, using an accepted system of standards (e.g. the Systemized Nomenclature of Medicine or the International Classification of Diseases). Please note that clinical and pathologic diagnoses are not always the same.**	I.b.2.	31
All	Tier 1	**Clinical. Patient clinical diagnoses (determined by medical history, physical examination, and analyses of a biospecimen) pertinent to the study being conducted.**	I.b.2.1.	24
All	Tier 1	**Pathologic. Patient pathologic diagnoses (determined by macro and/or microscopic evaluation of a biospecimen at the time of diagnosis and/or prior to research use) pertinent to the study being conducted.**	I.b.2.2.	32
All	Tier 2	Time between diagnosis and sampling. The time or range of time between disease diagnosis and sample acquisition.	1.b.2.3	
All	Tier 3	*Exposures. Neoadjuvant therapy, other current or past medical treatments or environmental factors that might influence the condition of the biospecimen (e.g. chemo-and radiation therapy, blood thinner, smoking status).*	I.b.3.	27, 31
All	Tier 3	*Reproductive status. The hormonal or reproductive state of the patients (e.g. pregnant, pre-pubescent, post-menopausal).*	I.b.4.	33
All	Tier 2	Patient demographic information. Demographic information that might be relevant to the condition of the biospecimens (e.g. age range, gender).	I.c.	34
All	Tier 2	Accrual scheme. Whether the biospecimens were obtained for the study being conducted or for a generalized collection such as a population-based biospecimen resource (i.e. retrospective or prospective procurement); whether any standard operating procedures (SOPs) were employed and whether these SOPs are available to others upon request. Reference any clinical trials relevant to the accrual scheme.	I.d.	35 – 38
All	Tier 2	Nature of the biobanking institution(s). The biobanking context in which the biospecimens were obtained (e.g. as part of an internal collection or a biospecimen-acquisition network); include name, location, and primary contact details such as email address or Web site and reference to any pertinent SOPs.	I.e.	35, 39
II. Acquisition				
Apply to	Tier #	Item Description	Item #	Example
All	Tier 1	**Collection mechanism and parameters. How the biospecimens were obtained (e.g. fine needle aspiration, pre-operative blood draw).**	II.a.	40 – 42
Tissue	Tier 3	*Time from cessation of blood flow in vivo to biospecimen excision/acquisition. The time or range of times that the biospecimens were ischemic in the body.*	II.b.	43
All	Tier 2	Time from biospecimen excision/acquisition to stabilization. The time or time-range between when the biospecimens were obtained (e.g. blood drawn or tumor surgically removed) and when they were stabilized. *For postmortem biospecimens*, list the postmortem interval range (i.e. the time from death to stabilization of the biospecimen).	II.c.	22, 44 – 48
All	Tier 2	Temperature between biospecimen excision/acquisition and stabilization. The temperature or range thereof at which biospecimens were kept between when biospecimens were obtained (e.g. blood drawn or tumor surgically removed) and when they were stabilized. *For postmortem biospecimens*, the temperature at which the cadaver was stored during the postmortem interval.	II.d.	45, 48 - 50
Fluid	Tier 2	Collection container. The kind of tube into which biospecimens were captured as they left the body.	II.e.	51 – 53
III. Stabilization/Preservation				
Apply to	Tier #	Item Description	Item #	Example
All	Tier 1	**Mechanism of stabilization. The initial process by which biospecimens were stabilized during collection (e.g. snap or controlled-rate freezing, fixation, additive (heparin, citrate, or EDTA), none).**	III.a.	54 – 56
All	Tier 1	**Type of long-term preservation. The process by which the biospecimens were sustained after collection (e.g. freezing and at which temperature; formalin fixation, paraffin embedding; additive; none). Please note, this might or might not differ from the mechanism of stabilization.**	III.b.	11, 57, 58
All	Tier 1	**Constitution and concentration of fixative/preservation solution. The make-up of any formulation employed to maintain the biospecimens in a non-reactive state (e.g. 10 percent neutral-buffered formalin or 10 USP Heparin Units/mL).**	III.b.1.	59, 60
Tissue	Tier 2	Time in fixative/preservation solution. The time or range thereof that biospecimens were exposed to the preservation medium.	III.b.2.	61, 62
Tissue	Tier 2	Temperature during time in preservation solution. The temperature of the medium during the preservation process.	III.b.3.	46
Fluid	Tier 2	Aliquot volume. The amount in each liquid biospecimen sample.	III.c.	60
Tissue	Tier 2	Specimen size. The approximate size or weight of solid biospecimen samples processed(e.g. cubes approximately 0.5 cm on a side, 0.5 gram).	III.d.	63
IV. Storage/Transport				
Apply to	Tier #	Item Description	Item #	Example
		Storage parameters. The conditions under which the biospecimens were maintained until analysis.		44, 64, 65
All	Tier 1	**Storage temperature. The temperature or range thereof at which the biospecimens were maintained until distribution or analysis.**	IV.a.1	44, 64 – 66
All	Tier 1	**Storage duration. The time or range thereof between biospecimen acquisition and distribution or analysis.**	IV.a.2.	44, 63, 64, 66, 68 – 70
All	Tier 2	Storage details. Other conditions under which specimens were maintained during storage (e.g. to minimize oxidation).	IV.a.3.	44, 63
All	Tier 3	*Type of storage container. The vessel in which biospecimens were kept.*	IV.a.4	53, 59, 70
All	Tier 3	*Type of slide. The microscope slides to which biospecimens were affixed.*	IV.a.5	71
		Shipping parameters. The conditions to which biospecimens were exposed during each shipment or inventory management.		44, 72
All	Tier 1	**Shipping temperature(s). The temperature or range thereof at which biospecimens were maintained during each shipment or relocation.**	IV.b.1.	72, 73
All	Tier 2	Shipping duration. The time, estimate, or range thereof that the biospecimens spent in shipment each time they were transported.	IV.b.2.	72, 73
All	Tier 3	*Type of transport container. The type of vessel (e.g. pre-manufactured shipping container, polystyrene box) and the packing material in which the biospecimens were transported.*	IV.b.3.	
All	Tier 3	*Shipping parameters. Other conditions under which the biospecimens were transported (e.g. vacuum sealing, desiccant, packing material). Please note any deviations from standard operating procedures that might influence the condition of the biospecimens (e.g. shipping anomalies that exposed paraffin blocks to high temperatures).*	IV.b.4.	
		Freeze-thaw parameters. The conditions to which biospecimens were subjected during any thaw events.	IV.c	44
Fluid	Tier 2	Number of freeze-thaw cycles. The number, estimate, or range thereof of thaw-refreeze events to which biospecimens were subjected prior to analysis.	IV.c.1.	70, 74, 75
Fluid	Tier 3	*Duration of thaw events. The amount of time or range thereof the biospecimens spent thawed prior to the final thaw before processing.*	IV.c.2.	76
Fluid	Tier 3	*Time from last thaw to processing. The time or range of times between unfreezing and analysis.*	IV.c.3.	
All	Tier 3	*Temperature between last thaw and processing. The temperature at which biospecimens were kept between unfreezing and analysis.*	IV.c.4.	77
V. Quality Assurance Measures Relevant to Processing Prior to Analyte Extraction and Evaluation of the Extracted Analyte				
Apply to	Tier #	Item Description	Item #	Example
All	Tier 1	**Composition assessment and selection. Any parameters that were used to evaluate and/or choose biospecimens for inclusion in the study.**	V.a.	78
All	Tier 2	Gross and microscopic review. The anatomical characteristics of the biospecimens in the study and the relevant qualifications of the individual performing the review (e.g. anatomist, pathologist, hematologist, microbiologist, or researcher).	V.a.1.	
Tissue	Tier 2	Proximity to primary pathology of interest. Whether the biospecimen was taken from a region adjacent to or distal from another region of interest, such as a tumor or area of necrosis. Give approximate distances if known.	V.a.2.	79, 80
All	Tier 2	Method of enrichment for relevant component(s). The method by which pertinent portions of the biospecimen were separated from the rest of the biospecimen (e.g. laser-capture microdissection of tissue, block selection for region of lesion, centrifugation of blood).	V.a.3	81, 82
All	Tier 2	Details of enrichment for relevant component(s). The parameters used to separate pertinent portions of the biospecimen from the rest of the biospecimen, if applicable (e.g. centrifugation speed and temperature).	V.a.4	83
Tissue	Tier 3	*Embedding reagent/medium. Any formulation used to enclose the biospecimens (e.g. paraffin).*	V.b.	84
All	Tier 2	Quality control and assurance measures. Any methods used to assess the quality of the biospecimens relevant to the biomolecular analyte, when these methods were employed (e.g. prior to long-term storage or immediately before experimental analysis), and the results (e.g. RNA integrity number, hemolysis assessment).	V.c	31, 85