



NNTC Request Processing and Fulfillment Rubric

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Process Overview

NNTC applications proceed through three main stages: **DCC Screening**, **Application Review**, and **Request Fulfillment**. After submission, an application must complete DCC Screening and receive approval through Application Review before Request Fulfillment begins.

Figure 1 summarizes the overall request process. **Figure 2** shows how the assigned **Request Complexity** Level affects Application Review and Request Fulfillment timeframes.

Figure 1: NNTC Request Process Overview

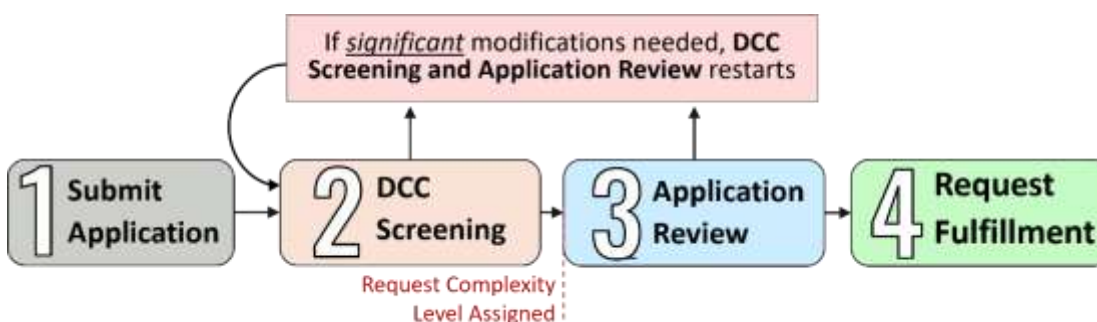
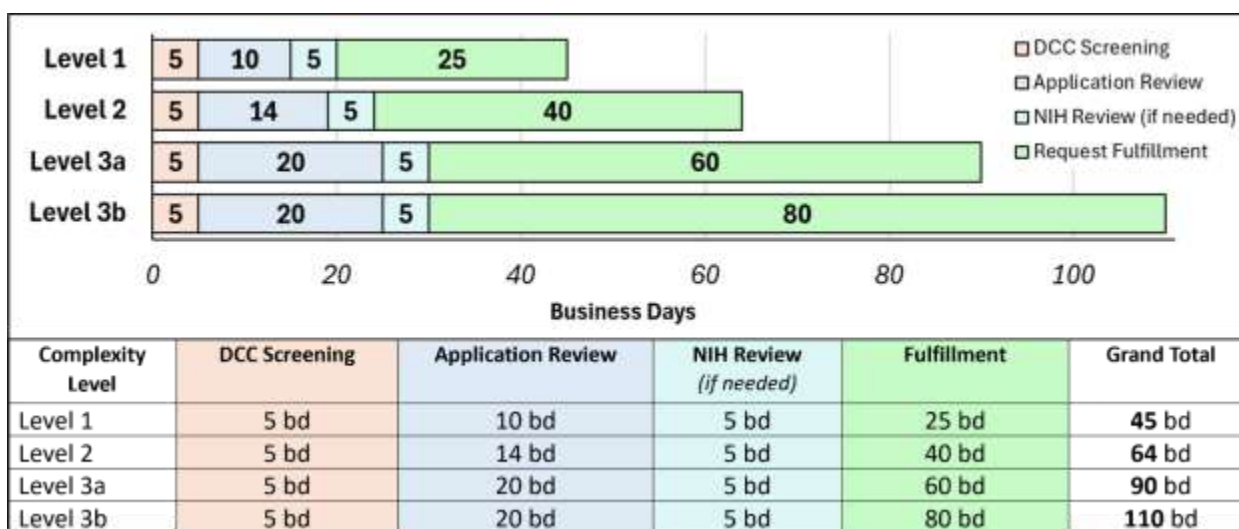


Figure 2: NNTC Review and Fulfillment Timeframes, by Complexity Level (bd=business days)



Note: The NNTC aims to fulfill sample requests according to the timelines outlined in this figure. These timelines are based on ideal conditions. However, real-world conditions may affect actual fulfillment timelines (e.g., length of existing request queue). See the [Request Fulfillment section](#) for further information.

Note: CHARTER is governed by a standalone grant mechanism. As such, requests involving CHARTER specimens and/or data are not bound by the NNTC-defined timeframes specified in this document. CHARTER makes every effort to review and fulfill requests as expeditiously as possible.

Please note that all requests submitted to the NNTC are processed by the Data and Coordinating Center (DCC) in the order in which they are received. This document outlines the process for how applications to the NNTC will be processed following submission. If you have questions prior to submitting your request, please do not hesitate to contact nntc@emmes.com to reach the DCC.

Application Submission

The first step in the NNTC Application Review and Fulfillment process is submission of the application itself. This step is critical for determining request review and fulfillment timelines.

a. Create an account

New Users: If you do not already have an account with the NNTC, you must submit a request for credentials via the study website (www.nntc.org). The DCC will create your credentials within 2 business days.

Existing Users: Use your DCC-provided credentials to [log in](#) to the secure portion of the study website to begin your application submission process.

b. Ensure that your application is complete and well-justified

Use a **copy of the Request Processing Checklist** as you prepare your application to **ensure that your request is clear, complete, and well-justified**. To document that you have reviewed, understood, and followed the checklist, you must submit a signed copy of the Request Processing Checklist as part of your application.

Requestors **must submit applications that are well-justified and include sufficient details to support the specimens requested in your application** (e.g., study group sizes, numbers, and types of specimens being requested, rationale, study design, experimental methodologies, etc.). The Request Processing Checklist, Concept Outline templates, as well as the Request FAQ document are helpful resources that may be found on the [NNTC website](#).

DCC Screening and Application Review

The DCC will perform screening and review of your application before assigning a Request Complexity Level. Clinical Sites will perform Application Review of each application to ensure it is complete and scientifically justified before fulfillment may begin.

NNTC Request Processing and Fulfillment Guidelines

To ensure timely completion of Application Review, applicants should try to answer any questions from the DCC within **2 business days**. Delays in responding will add time to the review of your application.

a. DCC Screening

First, the DCC reviews the application to verify that all required elements of the application package have been provided and are complete. The DCC allows up to **5 business days** to complete this phase of their review. This timeline assumes that the requestor adheres to responsiveness requirements outlined above, and that no substantive revision is needed.

Note: Please see the Request Processing Checklist for a comprehensive checklist detailing the materials/information that comprise a complete and clear application to the NNTC.

b. Assignment of Request Complexity Level

After DCC Screening is complete, a “**Request Complexity Level**” is assigned. The complexity level is determined by request size, complexity, and other factors. The Request Complexity Level drives timelines for the remaining Request Review and Fulfillment processes. Once assigned a Request Complexity Level, the application proceeds through the Application Review process, during which it will be reviewed by the NNTC Sites and other subject matter experts (SMEs), as applicable.

Please see [Appendix A](#) for a full table including Request Complexity Level criteria and the associated timelines for the remaining Review and Request Fulfillment processes.

c. Application Review

Once your application is assigned a Request Complexity Level, NNTC Site PIs and other SMEs, as applicable, begin their review of your application according to the timelines presented in [Appendix A](#).

During Application Review, NNTC Sites and other SMEs (includes site staff with specific expertise in a research area that overlaps with the science in the application) confirm whether their Site has donors/specimens that match the needs of your request and Site PIs and other SMEs review the scientific merit of the application (e.g., study rationale, design, proposed methodology, etc.). Any feedback from this stage of review will be routed to you by the DCC.

Note: If your application includes a request for neuroimaging data, NNTC’s neuroimaging subject matter experts will also contribute to the [review](#) of your application.

All questions from the review committee must be adequately addressed before your request is approved. NNTC expects that requestors will respond to inquiries relating to their request within 2 business days of receipt. Delays in responding will add time to the review of your application.

d. Examples of feedback you may receive during Application Review

Over the course of Application Review, you may receive feedback regarding your application. Examples include, but are not limited to:

- *Technical:*
 - The particular methodology you plan to use may not be feasible with the specimens you requested. In this case, the reviewers may ask you to revise and resubmit your application as a proof-of-concept (Level 1) request before proceeding with a more complex request.
- *Clarification:*
 - You may be asked questions about an element of your request that may be inconsistent with the rest of your application. For example, if your request is focused on the use of cardiac specimens and your group definitions include neurocognitive inclusion/exclusion criteria, you may be asked to explain how the neurocognitive criteria are relevant to your application
 - You may be asked to consider alternate brain regions for your request if the regions requested are not adequately justified, in short supply, and/or require extensive preparation or dissection.

e. Resolving delays in NNTC review of applications

If the rubric-defined review window for your application is more than 72 hours past-due, NNTC's alternate workflow comes into effect, as follows:

- If your application has three or more approvals, then your application will be considered approved.
- If your application has fewer than three approvals, one of the DCC co-PIs and/or NIH will provide the final approval decision for your application.

f. NIH review of rejected applications

If an application is rejected by Site PI reviewers during Application Review, representatives from the NIH will review the application and Site PI reviews. NIH staff will consult with the Site PIs, DCC, and applicant during this review process. NIH staff will then

make a final decision regarding the application. This NIH review will occur within 5 business days following any rejection decision from the Site PIs.

g. NNTC reviewer recusal

For typical applications, all NNTC Site PIs contribute to the review and approval process. In the event that an NNTC Site PI considers their role on the proposed research project as a partner or a collaborator, that PI will recuse themselves from the review of the corresponding application. In any other case where reviewer recusal may be appropriate, the determination of the need for recusal is left to Site PI judgement.

h. Revising an application during Application Review

Requesters should anticipate that their request may require some modification or clarification during Application Review. If your application requires modification, the NNTC will determine whether the modifications required are “significant” or “minor”. In all cases, the requester must accommodate all requested modifications.

If your application requires significant modifications, your modified (or new) application will go back to the beginning of the Application Review step and will re-enter the review process once the revised application is submitted.

If your application requires only minor modifications, your application will be considered approved *once you have addressed all modifications requested*. Applications requiring only minor modifications will not return to the beginning of the Application Review step.

The NNTC DCC is available to assist you with your application. If you have questions regarding request feasibility, scientific rationale, and/or complexity when preparing your application or during Application Review, you may request guidance from the DCC and/or Clinical Sites. The DCC can be reached during normal business hours at nntc@emmes.com. If you contact the DCC outside of business hours, someone from the DCC will get back to you within 2 business days.

Request Fulfillment

a. Shipping Accounts

In order to receive NNTC specimens, you will be asked to establish both FedEx and UPS accounts in order to facilitate shipments originating from NNTC centers. You may be asked to generate a shipping label to provide to the biorepository fulfilling the order. This will assure that the address and account information are correct for the shipment.

b. Request Fulfillment timelines

Once an application has been approved during Application Review, Request Fulfillment begins. Request Fulfillment times are driven by the application's assigned Request Complexity Level. **Request Fulfillment timelines in [Appendix A](#) start after an application is approved in the Application Review step.**

c. Communicating variance from estimated timelines

The NNTC aims to fulfill sample requests according to the timelines outlined in [Appendix A](#). These timelines are based on ideal conditions; however, real-world conditions may affect actual fulfillment timelines. Examples of such factors include, but are not limited to:

- Some sites require execution of a separate Material Transfer Agreement (MTA) before specimens can be provided. The fulfillment clock will not begin for these Sites until the MTA has been executed for any given request.
- Length of existing request queue (i.e., the number and complexity of previously approved requests that are in the process of fulfillment).
- Site demand and capacity for Request Fulfillment (e.g., local personnel are out on vacation, out sick, fulfilling multiple complex requests)
- Requirement for non-NNTC services to process samples (e.g., your sample requires sectioning by an external microtomy lab)
- Some Clinical Site pathologists may have clinical workloads that could introduce some delays in fulfillment timelines (e.g., pathologists may need to accommodate clinical responsibilities such as processing of tumors, surgical specimens, etc. that would take priority over fulfillment of NNTC requests.
- Standing Requests: Some requests must be fulfilled by prospective collection of certain specimen types, as autopsies occur. In these cases, fulfillment times will vary and unlikely to follow fulfillment timeframes outlined in [Appendix A](#).

- Analysis requests are evaluated on a case-by-case basis, due to the potential complexity of analyses being requested. Review and fulfillment timelines for these types of requests are determined on an ad hoc basis.

The NNTC prioritizes open and transparent communication about deviations from the request fulfillment timelines provided in [Appendix A](#).

d. Requestor strategies to optimize Request Fulfillment timelines

There are a few ways to optimize your application's review and fulfillment timelines.

i. Minimize request complexity

Applications with a lower Request Complexity Level are subject to notably quicker review and fulfillment timelines. As such, there is an operational advantage to designing a request to minimize parameters relevant to Request Complexity Level determination (e.g., number of donors, number of specimen/preparation types, etc.).

ii. Specify staging for Request Fulfillment

To help avoid any timing concerns for receipt of specimens, the NNTC advises that all investigators carefully consider how specimen provision might be staged, such that critical specimens are received first, with remaining specimens provided at a later date. These details are important to include in your application. The NNTC encourages investigators to contact the DCC at nntc@emmes.com with any questions about how to best incorporate staging into an application.

If the NNTC and a requestor are unable to align on recommendations for fulfillment staging and other options to explore alternate accommodations have been exhausted, the NNTC must either approve or deny the request.

iii. Fully justify the inclusion of any virally suppressed donors.

Any request that includes suppressed donors will require more rigorous review by the Executive Committee, because of the scarcity of such donors in the NNTC cohort. If suppressed donors are not essential for the conduct of your research, the NNTC recommends you carefully consider whether this can be removed as a criterion included in your request.

iv. Fully justify the inclusion of any small or anatomically scarce regions.

Any request that includes suppressed donors will require rigorous justification and review, because of the scarcity of such donors in the NNTC cohort. If suppressed donors

are not essential for your research project, the NNTC recommends carefully considering whether this criterion can be removed from your request.

v. Consult resources on the NNTC study website

Consult the FAQ and related resources provided by the DCC on the study website for further suggestions and information.

vi. Include power calculations to justify group sizes for all requests, except Level 1 pilot/proof of concept studies

The NNTC reviews all applications to ensure that appropriate statistical justification (e.g., power calculations) is provided to support requested group size(s) and number of specimens requested. If adequate statistical justification is absent or inadequate, your application may be returned to you for modification.

e. Requesting additional metadata after request is fulfilled

If you have a need to request additional metadata after your NNTC request is fulfilled, please reach out to nntc@emmes.com regarding your request. If determined to be a reasonable ask for additional metadata, a new application will not be required. If the ask is determined to be more substantive, you may be asked to submit a new application.

f. Regarding use of any surplus specimen amounts

If you have a remainder of any NNTC specimen(s) received and have any intent to utilize these specimens for additional research not included in your original application, you must contact the NNTC DCC at nntc@emmes.com to provide rationale about the proposed use of remaining materials. The DCC will advise as to whether a new application is required in your case. NNTC reviewers will expedite review of such requests as much as possible (target review timeline will be the same as for a Level 1 request).

Returning Experimental Data to NNTC

All requestors must return any experimental data generated from specimens obtained from the NNTC. The NNTC Data Coordinating Center (DCC) coordinates, stores, and makes accessible all de-identified data obtained from the NNTC subjects and specimens derived from the subjects. All requestors agree to the following when signing the NNTC User Agreements, a required component of all applications:

- The NIH expects NNTC recipients to provide the DCC with electronic copies of all data within twelve (12) months of receiving the materials or within a month of publication of data using samples from NNTC, following an update at 12 months.
- Continued reporting to the DCC should occur at least annually as the analysis progresses until the analysis is completed.
- Data can be embargoed to prevent its release until publication. All data will be referenced to the investigator and publication when relevant.
- For indexing purposes, the NNTC expects recipients to submit data in a specific format with an NNTC subject ID number; forms for this submission will be provided upon approval of the resource request.
- Data will be provided to the NNTC DCC in a format to be determined in conjunction with the DCC depending on the type of data. The DCC will provide templates and examples to the requestor upon approval of the request, followed by annual reminders.
- High-throughput data (genomic, gene expression, proteomic, and metabolomic data) should be submitted to the appropriate NCBI repository (dbGap {<https://www.ncbi.nlm.nih.gov/gap/>} for genomic, GEO {<https://www.ncbi.nlm.nih.gov/geo/>} for gene expression, other data types if/as they become available), using their respective formats. Appropriate links to the data should be provided to the DCC. Other high-throughput as well as medium- and low-throughput datasets and associated metadata are to be submitted to the DCC; working with the DCC to determine the best format to transfer data.

Important: Following receipt of NNTC specimens for a request, all requestors must submit an annual progress report(s) to the DCC for prior requests (including a description of data obtained and a timeline for completion of the project), as well as experimental data from any completed projects, before additional applications to the NNTC will be processed.

APPENDIX A: Request Complexity Level Criteria, with Review, Request Fulfillment Timeframes

L V L	Request Details	Request Complexity Considerations	Review Period ^D	Request Fulfillment ^D
Level 1	- A <u>pilot project specimen request</u> (see definition, Definitions and Key Terms table) - A <u>proof-of-concept specimen request</u> (see definition, Definitions and Key Terms table) - A <u>data-only request</u> that includes only centrally maintained data elements. Neuroimaging data requests, provided only NNTC neuroimaging is requested, in the existing NNTC data structure/format. - All requests for <u>Letters of Support</u> will be fulfilled by the NNTC on Level 1 timelines. (see definition, Definitions and Key Terms table)	<i>ALL of the following are required:</i> ≤12 specimens in total (except for requests for Letters of Support). Note that a digital slide counts as a specimen. - Tissue/aliquot amounts at or below standard amounts listed in Appendix B ^A - NO small or anatomically limited brain subregions^B - NO complex dissection or custom preparation - Does not require clinical sites to perform microtomy	No more than 10 business days after Request Complexity Level is assigned.	Shipments complete within 25 business days of application approval.

LVL	Request Details	Request Complexity Considerations	Review Period ^D	Request Fulfillment ^D
Level 2	- A <u>specimen request</u> and associated clinical data that meets one or more of the following criteria: - Demonstrated experience with the proposed technique (e.g., publication or preliminary data) - History of previous successful use of NNTC specimen resources^E - A <u>data-only request</u> that requires elements not maintained centrally, and/or requires calculations to be performed, and/or requires specific subject matter expertise.	<i>ALL of the following are required:</i> ≤ 50 specimens total. Note that a digital slide counts as a specimen. - Tissue/aliquot amounts that are less than or equal to standard amounts listed in Appendix B,^A - NO small or anatomically limited brain subregions^B - NO complex dissection or custom preparation	No more than 14 business days after Request Complexity Level is assigned.	Shipments complete within 40 business days of application approval.
Level 3a	A <u>specimen request</u> along with associated clinical data that exceeds Level 2 requirements and limits.	<i>ALL of the following are required:</i> - Does not exceed 100 specimens total^C. Note that a digital slide counts as a specimen. - NO small or anatomically limited brain subregions^B - NO complex dissection or custom preparation	No more than 20 business days after Request Complexity Level is assigned.	Shipments complete within 60 business days of application approval.

LVL	Request Details	Request Complexity Considerations	Review Period ^D	Request Fulfillment ^D
Level 3b	A <u>specimen request</u> along with associated clinical data that exceeds Levels 2 and 3a requirements and limits.	<i>ALL of the following are required:</i> - Does not exceed 100 specimens in total^C. Note that a digital slide counts as a specimen. - May require small or anatomically limited brain subregions^B, - May require a complex dissection or custom preparation	No more than 20 business days after Request Complexity Level is assigned.	Shipments complete within 80 business days of application approval.

Footnotes: Important – Please Read

^A – A request application that includes tissue/fluid amounts in excess of what is stated in [Appendix B](#) for any of the experimental methodologies listed must include specific justification supporting the specimen amount being requested.

^B - Anatomically-limited brain regions include nucleus accumbens, basal ganglia, hippocampus, striatum, choroid plexus, brain stem nuclei. Anatomically-limited regions/specimens also include brain regions and any tissues or samples that are not part of the required NNTC dissection; are not consistently available; and/or are extremely difficult to find, collect, and process from all participants.

^C - Applications requesting more than 100 total specimens will be evaluated on a case-by-case basis and will not held to any rubric-defined review and fulfillment timelines. All applications requesting more than 100 specimens must include a comprehensive justification for the number of specimens requested (i.e., power analysis(es) or other justification) and for any anatomically-limited brain region or other tissue.

^D – **CHARTER REQUESTS:** CHARTER is governed by a standalone grant mechanism. Therefore, requests involving CHARTER specimens and/or data are not bound by the NNTC-defined timeframes specified in this document. CHARTER makes every effort to review and fulfill requests as expeditiously as possible.

^E – “History of previous successful use of NNTC specimen resources” requirement is satisfied when a requestor has returned data to NNTC (per Data Use Agreement requirements), thereby demonstrating successful use of the same/similar technique with previously provided NNTC specimens. If you are submitting a new request before your previous experimental data is due, please include any available preliminary data to support past successful use of NNTC specimens/resources.

NNTC Request Processing and Fulfillment Guidelines

APPENDIX B: Standards for provision of NNTC tissues and fluids

Method	Standards, by Method
Protein isolation for immunoblot or related methods	≤ 100 mg of tissue per protein examined
Mass Spectrometry (e.g., for proteomics, metabolomics, drug quantification)	50-100 mg
DNA or RNA isolation (e.g., for PCR, next-gen sequencing, etc.)	≤ 50 mg
Single nucleus RNA/ATAC-seq (and related methods)	100 – 200 mg (higher end if white matter only)
Spatial transcriptomics	Dependent on procedure used
Assays on frozen tissue blocks (e.g., laser capture microdissection, immunofluorescence)	500 mg (1 cm x 1 cm x 0.5 cm)
Slide-Based Assays on FFPE (e.g., <i>in situ</i> hybridization, immunohistochemistry, spatial transcriptomics)	Sufficient tissue for ≤ 6 sections per condition Standard section thickness is 4-6 µm.
Specimen/Tissue type	Standard Preparation, Volume Standards
PBMCs	• 5 x 10⁶ cells • Majority are frozen as non-cryopreserved (non-viable) only • Recent collection includes cryopreserved (viable)
• Plasma • Serum • CSF • Urine	• 0.5 ml aliquot

APPENDIX C: Abbreviations

Abbreviation	Description
BD	Business Days
CIDI	Composite International Diagnostic Interview
CHARTER	CNS HIV Anti-Retroviral Therapy Effects Research
CNTN	California NeuroHIV Tissue Network
CSF	Cerebrospinal fluid
DCC	Data Coordinating Center
FAQ	Frequently Asked Questions
FWA	Federalwide Assurance
FFPE	Formalin-Fixed Paraffin-Embedded Sections
HIV	Human Immunodeficiency Virus
ID	Identifier
MHBB	Manhattan HIV Brain Bank
MTA	Material Transfer Agreement
NIH	National Institutes of Health
NNAB	National Neurological AIDS Bank
NNTC	National NeuroHIV Tissue Consortium
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PRISM	Psychiatric Research Interview for Substance and Mental Disorders
PWH	People with HIV
PWoH	People without HIV
RNA	Ribonucleic acid
SME	Subject Matter Expert
SUD	Substance Use Disorder
TNRC	Texas NeuroHIV Research Center
WASHU	Washington University in Saint Louis

APPENDIX D: Definitions and Key Terms

Term	Description
DCC	The Data Coordinating Center (DCC) is responsible for management of the review and approval process for applications. All questions about your request, please contact nntc@emmes.com .
Clinical Sites	The NNTC Clinical Sites are the centers that contribute to the NNTC. Clinical Site PIs are the primary reviewers/approvers of NNTC applications, and Clinical Sites are responsible for fulfillment of all NNTC requests.
Pilot request	Any request that meets all of the following criteria: • 1-12 total specimens (note that a digital slide counts as a specimen) • Does not include specimens from anatomically limited regions (e.g., nucleus accumbens) • Does not include specimens that require complex dissection or special preparation (e.g., microtomy)
Proof-of-Concept request	Any request that meets all of the following criteria: • 1-12 total specimens (note that a digital slide counts as a specimen) • Includes scientific methodology that requires validation using NNTC specimens before proceeding to a larger scale request. • Does not include specimens from anatomically limited regions (e.g., nucleus accumbens) • Does not include specimens that require complex dissection or special preparation (e.g., microtomy)
Letter of Support	NNTC Letters of Support are provided to requestors to confirm NNTC's intent to support a proposed plan of research. These letters are most commonly provided for potential requestors who must first secure funding. <u>Note</u> : Letters of Support are intended to document the NNTC's intent to support the research. However, requesters who have received Letters of Support must submit applications that undergo the full Application Review and Approval process before any specimens and/or data may be distributed.
Specimen	A quantity of tissue, blood, or other biologically derived material. Note that a digital slide counts as a specimen.