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# Toward Improving Practices for Submission of Diagnostic Tissue Blocks for National Cancer Institute Clinical Trials

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## ABSTRACT

**Objectives:** *The National Cancer Institute (NCI) National Clinical Trials Network performs phase II and III clinical trials, which increasingly rely on the submission of diagnostic formalin-fixed, paraffin-embedded tissue blocks for biomarker assessment. Simultaneously, advances in precision oncology require that clinical centers maintain diagnostic specimens for ancillary, standard-of-care diagnostics. This has caused tissue blocks to become a limited resource for advancing the NCI clinical trial enterprise and the practice of modern molecular pathology.*

**Methods:** *The NCI convened a 1-day workshop of multidisciplinary experts to discuss barriers and strategic solutions to facilitate diagnostic block submission for clinical trial science, from the perspective of patient advocates, legal experts, pathologists, and clinical oncologists.*

**Results:** *The expert views and opinions were carefully noted and reported.*

**Conclusions:** *Recommendations were proposed to reduce institutional barriers and to assist organizations in developing clear policies regarding diagnostic block submission for clinical trials.*

In the era of precision medicine there are competing demands placed on the use of diagnostic formalin-fixed, paraffin-embedded tissue blocks for analytical purposes. In addition to their routine use for standard-of-care pathology diagnostics, they may be required for biomarker studies to determine clinical trial eligibility or treatment stratification of patients. They are also often needed for scientifically and statistically justified correlative biomarker studies that address secondary clinical trial objectives. Pathologists at many institutions are attuned to the clinical trial demands but are often reluctant to distribute blocks outside of their institution, due to justifiably perceived medicolegal concerns that blocks may be lost, exhausted, or destroyed in the course of their use in research studies and unavailable if needed for future patient care.

Prompted by an apparent decline in the number of blocks being submitted for clinical trials, more than 600 pathologists completed a survey administered by the College of American Pathologists (CAP) in 2011 regarding block submission in the clinical trial setting.<sup>1</sup> Results indicated that only 18% of institutions send a block to requesting trial researchers. Furthermore, if tumor is confined to only one block, more than 80% of pathology departments indicated that they would not

release the block. In contrast, over 70% of pathology departments surveyed agreed that they would send some tissue block alternative, such as tissue slides. A minority of institutions (14%) actually cited an institutional policy (often originating in the pathology department) that prohibited the release of blocks for research studies.

National Clinical Trials Network (NCTN) oncology groups conduct treatment trials supported by the National Cancer Institute (NCI). These trials include randomized phase III, phase II, and precision medicine trials across the United States, enrolling approximately 20,000 patients at more than 2,000 sites each year.<sup>2</sup> NCTN trials often include biospecimen collection and biomarker testing, categorized as *integral*, *integrated*, and *secondary* correlative studies. Integral biomarkers are required for the trial to proceed (eg, to determine a patient's eligibility or arm assignment). If a clinical block is not submitted for integral biomarker studies, patients cannot be enrolled, and the trial is at risk of being statistically underpowered. Integrated biomarkers are those needed to address an end point of the trial. If a clinical block is not submitted for integrated biomarkers, the trial's biomarker-based science is jeopardized. Tissue can also be collected and banked for future secondary correlative studies. Most patients consent to this as an option, for future research beyond the immediate trial objectives. Because exact specimen requirements for future studies are unknown and because material may be stored for long after the trial conclusion, tissue blocks are particularly important for supporting future research.

## Materials and Methods

To identify ways to improve block submission, the NCI held a "Workshop on Improving Practices for the Submission/Release of Tissue Blocks for NCTN Clinical Trials" on June 16, 2016. Current trial, laboratory, regulatory, legal, and ethical policies and procedures influencing block submission for clinical trials were discussed in an effort to raise awareness and recommend solutions.

## Results

### NCTN Clinical Trial Block Submission Procedure (NCTN Biobankers)

NCTN biobanks are uniquely positioned to collect, store, and provide researchers with quality biospecimens that are well annotated with demographic, clinical, and

long-term follow-up data from patients enrolled in NCTN clinical trials. NCTN biobanks collect biospecimens in real time from many sites participating in NCTN trials, for use in NCI-approved trial protocols. Biospecimens remaining after integral and integrated trial studies are completed may also be used for future secondary correlative studies according to an established NCI NCTN scientific merit access process. NCTN biobanks are held to high ethical, scientific, and patient safety standards. Strict rules govern the provision of biospecimens to researchers. NCTN biobanks follow CAP Laboratory Accreditation Program (LAP) guidelines for biospecimen release and take all measures to safeguard tissue preservation and avoid depleting blocks.

For some trials, clinical sites may offer and NCTN biobanks may allow the submission of alternate specimens such as unstained tissue section slides (cut at 6  $\mu$ m or 10  $\mu$ m for immunohistochemistry [IHC] or nucleic acid extraction, respectively), tissue cores, tissue scrolls, or even tissue-derived nucleic acids. This material may fulfill the tissue block submission requirement, but as stated by many participants at the workshop, alternative biospecimens to block submission may be suboptimal for many reasons. Many trial correlative studies are performed years after initial submission to the biobank. The preservation of molecular characteristics in a tissue specimen is best achieved by storing tissue blocks and sectioning just prior to analysis because antigen and nucleic acid degradation from ambient air exposure (oxidation) occurs slower in tissue blocks than cut tissue slides.<sup>3-10</sup> Many IHC studies require freshly cut slides. Studies have shown that expression of many clinically relevant IHC markers in previously cut slides is significantly affected due to antigen loss over storage time (observed after just 12 weeks).<sup>11-13</sup> While some facilities have attempted to preserve molecular integrity of cut tissue slides by vacuum sealing and cold room storage, this entails considerable cost, and there are little or no controlled data to suggest that this strategy is effective.<sup>14</sup> Moreover, slide storage (even in ambient conditions) is more expensive from a biobanking perspective. NCTN biobanks report that submission of a single block per patient consumes roughly 10 times less storage space than submission of a protocol-specified quantity of slides.

To avoid submission of suboptimal block alternatives, many NCTN trial protocols require initial block submission to the NCTN biobanks on a long-term basis but provide a transparent and expeditious block return policy. In these cases, NCTN biobanks may often obtain material (eg, slides, cores) from submitted blocks for approved trial-specified studies just prior to returning

blocks to the submitting institutions. Blocks needed for immediate patient care are returned in a timely manner.

### Importance of Block Submission for Clinical Trials and Biomarker Testing (Clinical Oncologists)

Oncologists from several large academic institutions emphasized the importance of block submission for clinical trials.

Many times, these individuals serve tripartite roles as caregivers, clinical trialists, and translational research scientists. As caregivers, their primary duty is to ensure that patients receive state-of-the-art clinical care. As an increasing number of biomarker-driven therapies are offered to patients, the availability of archived tumor tissue blocks for secondary diagnostic assessment is critical. Similarly, physicians who wish to enroll their patients on clinical trials are often required to submit tissue blocks for integral biomarker testing to determine eligibility.

In the context of the NCTN, biomarkers are categorized as integral, integrated, or biomarkers for secondary correlative studies.<sup>15</sup> Depending on the biomarker categorization, biospecimen collection may be required or optional for patient participation in an NCTN clinical trial. An integral biomarker study is defined as an assay or test that must be done in order for the trial to proceed or to support the primary analysis. Integral biomarker studies are inherent to the design of the trial and must be done on all participants, usually in real time. An integrated biomarker study is intended to validate a biomarker for use as an integral biomarker in future trials or clinical practice. Integrated biomarker studies test a specific hypothesis with a preplanned statistical design and are not hypothesis generating or exploratory. All other biomarker testing is for future secondary correlative studies.

As principal investigators of translation research studies, several participants cited examples where material submitted as block alternatives (slides and tissue block punches) yielded insufficient or suboptimal material (eg, DNA and RNA) needed for planned molecular and genomic studies. In fact, in some cases, the number of inadequate specimens was so large that no statistically significant conclusions resulted from the study. This not only affects the quality of science that can be performed in the context of clinical trials but also does not benefit those patients who consented to donate specimens for specific research purposes.

Moreover, when trial requirements allow for the submission of slides or other alternates in lieu of blocks, additional costs may be incurred to cut blocks, prepare slides, and ship boxes of heavy, fragile glass to the biobank. These additional costs may, in part, reduce the overall trial budget, hampering use of resources available to conduct the trial at the oncologist's institution.

### Institutional Policies on Submission of Blocks for Clinical Trials (Pathologists)

Academic and private pathologists from several institutions and private practice settings discussed their policies on block submission for trial eligibility and/or trial-based research (provided that such release and use have been properly consented) and presented various scenarios. Pathologists take their role as keepers and custodians of the blocks very seriously. It is important that the need for the block request is justified and understood by the pathologist. It should be emphasized that the intended research will be done to advance patient care and medical science. Pathologists have a role and responsibility in fostering this advancement; otherwise, material may be retained in storage for decades without use.

The CAP is a member association of board-certified pathologists that inspects and accredits medical laboratories under the auspices of the Centers for Medicare & Medicaid Services. Clinical laboratories accredited by the CAP must meet standards specified in the LAP checklists.<sup>16</sup> LAP standards not only are requirements for accredited laboratories but also provide guidance to pathologists on issues such as block release for NCTN trials.<sup>16</sup> CAP believes that, whenever possible, at least one block of diagnostic tissue should be preserved, intact, for the minimal retention time specified by appropriate custodianship laws and should not be used for research, education, quality control, or any other nondiagnostic activity. When this is not possible, such as in situations where only one diagnostic block is available, the laboratory director should ensure there are policies in place to preserve adequate amounts of diagnostic tissue for potential future clinical (diagnostic, prognostic, or predictive) use.<sup>17</sup> When only one block is available, the pathologist should determine if the block can be sent for research, provided some diagnostic material is kept by the pathology department at the submitting institution. The ANP.12500 Record Retention Phase II<sup>16</sup> (revised August 21, 2017) of CAP's Anatomic Pathology Checklist requires tissue in blocks, sufficient to support the diagnosis, be kept for 10 years and requires a written retention policy to preserve their integrity and the ability to retrieve them. Blocks must be documented, and records should show where and under what circumstances the block was stored. However, this requirement does not prevent a pathology department/site from sending a block or other blocks from the same patient's procedure for trials within those 10 years, provided some diagnostic tissue is kept.

As a matter of institutional policy, some pathology departments or medical centers mandate custodial retention of clinically acquired blocks as part of the permanent medical record and rarely will temporarily release them.



Others have a more open policy and either temporarily release the blocks or submit a block for permanent storage at an NCTN bank if multiple blocks with similar histologic features are available. Because a block is part of a pathology medical record case, block release may also be influenced by the opinion of the pathologist who handled the requested case. The amount of tissue, especially tumor, is often a limiting factor. Based on the amount of tumor in the block, the pathologist will determine whether a block can be provided. Utilization priority for blocks was stated to be (1) diagnosis, (2) molecular testing for treatment, (3) national trials research, and (4) translational research with biotech industries. While many pathologists felt that tissue slides were acceptable alternatives to tissue blocks, particularly when needed for specific and limited integral or integrated IHC-based studies, there was also agreement that submission of tissue cores often provides limited material that may not be of high quality and that the coring procedure itself can deface and compromise future clinical utility of diagnostic blocks. Specific reasons for denial to release a block (by either the case pathologist and/or institutional policy) include the following:

- Block retention that is necessary for cited regulatory compliance
- An increasing need for tissue blocks for personalized medicine molecular assays in the future
- Potential need for a block for patient enrollment in subsequent trials
- Perception that blocks will not be returned if requested

There is clearly a need for increased collaboration among the trialists, medical professionals, pathology departments, and biobanks. Successful collaboration requires improved understanding by all parties. Pathology departments should be transparent with the rules and processes governing the release of blocks. Trialists should be transparent regarding the rationale and justification for the requested block submission. Medical professionals should clearly communicate the pros and cons of block submission for clinical trials with their patients. Biobanks should be transparent regarding their policies for block retention and return. Both the medicolegal and the ethical implications of retaining or releasing blocks must be carefully assessed and workable, but flexible block policies must be established.

### Release of Paraffin Tissue Blocks and Patient Autonomy (Patient Advocates)

Some patients believe their tissue “belongs” to them and, by consenting to a trial, expect their tissue and data

will be used for research. Professionals, however, have a responsibility to weigh patient autonomy and patients’ clinical and trial benefit. Patients should be educated about biospecimen release policies for research. It is important for clinicians or research staff to clearly explain to patients the processes and policies governing disposition of their biospecimens, whether consent for research was provided or not. The possibility that blocks may be destroyed after certain periods of time (eg, 10 years) in accordance to current retention guidelines (eg, Clinical Laboratory Improvement Amendments [CLIA], CAP, or state government—whichever is more stringent) should be also discussed.

Workshop participants debated when and how to best discuss these issues with patients. If discussed before surgery, patients may be more focused on their illness and imminent procedure than future tissue use. If discussed during the surgical consent process, the message may be poorly absorbed by the patient (eg, additional text in an already lengthy consent document). Currently, most surgical consents are focused on adverse events, not the disposition of material obtained during surgery. Other potential methods for conveying messages about block stewardship to patients include a concise guideline document, newsletters, seminars, public service announcements, online videos, and a list of frequently asked questions.<sup>18-25</sup>

### Custody of Biospecimens: Custodianship and State Law Issues (Lawyers)

While consent is required for the collection of biospecimens, patients’ rights are less clear once their tissue has been removed. Patients have no legal right to direct that their block be sent for a trial and to an NCTN bank. In two lawsuits, *Moore v. Regents of University of California*<sup>26</sup> and *Washington University v. Catalona*,<sup>27</sup> the court decisions did not endorse any principle of law that patients have a “right” to control the disposition of their banked biological materials or to profit from the commercialization of their biological materials.

Tissues in clinically collected blocks are considered part of the medical record, and institutions are legally required to retain them for clinical care. State malpractice laws also influence tissue retention by institutions, with statutes of limitations varying by state. The State of New York requires block retention by institutions for 20 years.<sup>28</sup> As noted above, CAP<sup>16</sup> also provides guidelines regarding retention time for tissue blocks and slides **Table 1**. The ANP.12500 Record Retention Phase II<sup>16</sup> (revised August 21, 2017) of CAP’s Anatomic Pathology Checklist requires tissue in blocks to be sufficient to support keeping the diagnosis for 10 years at pathology departments and

**Table 1**  
Tissue Retention Standards for Blocks and Slides

Accrediting Body	Time to Retain, y	
	Blocks	Slides
CLIA, 2003 <sup>29</sup>	2	10
CAP, 2017 <sup>16</sup>	10	10

CAP, College of American Pathologists; CLIA, Clinical Laboratory Improvement Amendments.

requires a written retention policy to preserve their integrity and the ability to retrieve them. CLIA<sup>29</sup> regulations require that tissue blocks be retained for at least 2 years from the date of examination. Pathologists are custodians, and custodianship entails oversight responsibilities for the management and handling of tissue to benefit the patients.

### Ethical Issues Related to Biospecimens and Research Biopsy Specimens in Cancer Clinical Trials (Ethicists)

Medical institutions do not have an unconditional ethical obligation to release biospecimens obtained for diagnostic purposes to researchers, even if patients provided consent for leftover excised tissue to be used in research. Patient care is the primary obligation of medical institutions; if a determination is made that tissue needs to be retained for long-term diagnostic reasons, that determination governs. Thus, for example, CAP guidelines state that tissue should be retained for even longer than the typical 10-year retention period for some patients with metastatic disease.<sup>16</sup> Currently, a biospecimen request from the NCTN does not prevail over another researcher's request, provided the tissue was not collected specifically for the NCTN. Good institutional governance should include transparent policies that establish criteria and priorities for distribution of biospecimen materials remaining after diagnosis.

In addition to reasons specifically cited (see Institutional Policies on Submission of Blocks for Clinical Trials (Pathologists)), there are a number of other perceived reasons for a pathology department/site to keep a block:

- New biomarkers may be discovered in the future that can direct patient care or make the patient eligible for another trial.
- Uncertain diagnosis can be clarified years later with new tests.
- Recurrent tumor can be compared to primary tumor to determine whether it is a metastasis or a new primary.
- Testing of the primary tumor prompted by a new lesion may reveal a condition that affects family

members (eg, microsatellite instability testing and Lynch syndrome).

Medical institutions may attempt to make an ethical claim that their duty of beneficence toward patients (ie, the duty to promote the patient's health and welfare) triggers a professional responsibility to retain tissue blocks for patient care reasons. This duty to safeguard the block for patient care, it would be argued, will apply even when a patient has specifically requested that the block be sent to the NCTN or donated for trial research. In this notably paternalistic approach, the patient's clinical care, as assessed by the institution's collecting site, takes priority over the patient's autonomous and expressed preference to release the block for a clinical trial and/or to support research. The contrary ethical argument is that patient autonomy is a primary ethical principle that supersedes beneficence and overrides a treating institution's obligation to retain the block.

The fact that NCI-sponsored trials, like many other national clinical trials, are therapeutic research and that patients may potentially benefit from participation in these studies is often overlooked. It is important to note that all NCTN trials receive scientific and ethical review and are approved by the NCI. NCTN trials use tissue to evaluate a diagnostic or therapeutic intervention that could lead to improvements in the health or well-being of patients. Failure to submit blocks may prevent patients from enrolling and thus arguably may jeopardize their opportunity to derive therapeutic benefit. Beyond the possibility of personal benefit for research participants, failure to submit blocks has the societally unjust effect of undermining the entire clinical trial enterprise, diminishing both enrollment and effective progress, as well as increasing the chances the trials of promising therapies may have to close.

## Discussion

### Workshop Recommendations

- Cancer clinical trials have a high priority for tissue block utilization, second only to standard-of-care medical management. Pathology departments should have a written policy for the release of blocks for clinical trials, as long as trial physicians provide an appropriate and clear rationale for specimen use and proper patient medical management is not compromised.
- Pathology departments are custodians of patients' tissue and should honor patients' wishes, to the extent consistent with applicable laws and professional standards.

- During the patient consent and education process, clinicians and research staff should explain benefits vs possible risks incurred when a site sends a block to an NCTN bank (eg, material may not be available for future testing). An informed consent that explains these ramifications may allay pathologist concern about transparency as well as risk management.
- Pathology departments, clinical research coordinators, and oncologists should strive for transparent communication, specifically by confirming that proper approvals (eg, patient consent, institutional review board [IRB]) were obtained for tissue block release.
- Institutional pathologists and oncologists should communicate directly if blocks are requested for release. The rationale for block submission and the scientific rigor of NCTN trials should be discussed with site pathologists.
- Clinical trialists and biobankers should provide pathologists with the established NCTN biobanks' block return policy for clinical use.
- Pathology departments and NCTN biobanks should consider entering into a "trusted entity" agreement according to which the biobanks become agents of the collecting sites and maintain compliance with regulatory and patient care requirements.
- Oncologists, surgeons, and pathologists should consider the feasibility of obtaining an extra "research block." With this strategy, one block may be used for clinical trial research, while the remaining diagnostic block is preserved for clinical use.
- Pathologists in CAP LAP-accredited and other institutions need to be aware that the CAP requirement to retain blocks for 10 years does not prevent a site from submitting the block for clinical trials. As long as some diagnostic tissue is kept, "the restriction on release of blocks does not prohibit release of blocks for purposes of treatment, diagnosis, prognosis, etc., for patients on research protocols as long as release is consistent with patient privacy regulations (e.g. Health Insurance Portability and Accountability Act (HIPAA)) and applicable state and local regulations; and there is IRB approval, as applicable."<sup>16</sup>
- Laboratory accrediting organizations such as CAP and other regulatory agencies should reconcile block retention requirements and provide more specific guidance to pathologists in the context of patients consenting to clinical trials and whose blocks are requested by appropriately governed biorepositories, such as the NCTN biobanks.
- CAP and patient advocates should develop resources to educate academic and community pathologists and patients on issues related to block release for

NCTN and other nationally sponsored clinical trials. Both can assist in bringing this issue to a more public forum.

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