Emerging Issues in Tissue Allocation

Biomedical research generates novel information about cancer every day. New scientific capabilities, such as next generation sequencing, provide investigators new ways to study cancer biology, while growing numbers of clinical trials test advanced interventions, such as combined therapies and immunotherapies. These efforts have created increasing demand and need for human tissue samples.

Human tissue, however, can be difficult to procure, samples may be limited, competition for available tissue may be fierce, and maintaining some paraffin embedded tissue for future patient care purposes is desirable. Obtaining tissue from patients can be uncomfortable and with potential for risk. Common belief is that, first and foremost, the priority use of human tissue should be for diagnostic /clinical purposes. It is only after clinical need is met that tissue should become available for research purposes. Investigators desiring tissue for research may be at the patient's treatment institution, other institutions, or companies that develop drugs, devices, or companion diagnostics.

Tissue samples, whether for research or clinical diagnosis, are often housed in a biorepository, where biological materials are collected, processed, stored, and distributed in support of future scientific investigation. The biorepository assures the quality and manages the accessibility and distribution/ disposition of the biospecimens in its collection. Large cancer centers often have a shared resource that provides banked tissues to investigators while maintaining patient confidentiality. Pharmaceutical companies and other entities may also maintain their own biorepositories. In general, biorepositories are required to be overseen by a committee that governs how the tissue and other samples are allocated to investigators and reviews specific proposals to assure that tissue requests are appropriate for a proposed study. However, even though biorepositories can enable greater sharing of resources, there are not enough specimens to meet the demand. As a result, tissue allocation has become a growing issue for many clinical and translational investigators.

Tissue repositories, whether large or small, must develop best practices to handle the plethora of demands for these important and sensitive materials. These practices must balance the need to advance science with the requirement to comply with a complex set of regulations around tissue collection, processing, storage, and allocation. The Joint Commission, the federal government (Clinical Laboratory Improvement Amendments of 1988), the College of American Pathologists (CAP), hospitals, Institutional Review Boards (IRBs), and the Health Insurance Portability and Accountability Act (HIPAA) are all involved in the regulatory environment. In addition, numerous stakeholders—including clinicians, pathologists, clinical and translational investigators, academic institutions, the pharmaceutical industry, the National Cancer Institute, American Association for Cancer Research, CAP, patient advocacy groups and patients, IRBs, ethicists, and lawyers—have an interest in effective allocation of tissue samples.

The emerging challenges in tissue allocation include the implementation of institutional policies, contracting, relationships between academia and industry, patient informed consent, ethical standards, and costs. Input from all of the aforementioned stakeholders is needed to develop a comprehensive understanding of these challenges and to determine acceptable standards for tissue allocation.

On June 8, 2015, the National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of 26 of the world's leading cancer centers dedicated to improving the quality, effectiveness, and efficiency of care provided to patients with cancer, hosted the NCCN Policy Summit, *Emerging Issues in Tissue Allocation*, at the National Press Club in Washington, DC, to discuss the concerns around tissue allocation. This issue was initially raised by the Investigator Steering Committee that advises NCCN's Oncology Research Program (ORP). After determining that tissue allocation was a topic worthy of further review, NCCN established a Tissue Allocation Work Group to identify central or common problems and issues and to identify possible solutions.

Tissue Allocation Work Group members included co-chairs David L. Rimm, MD, PhD, Yale Cancer Center/Smilow Cancer Hospital, and Daniel Sullivan, MD, Moffitt Cancer Center; Al B. Benson III, MD, FACP, Robert H. Lurie Comprehensive Cancer Center of Northwestern University; Judith Carrithers, JD, MPA, CIP, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Jeffrey W. Clark, MD, Massachusetts General Hospital Cancer Center; Carolyn Compton, MD, PhD, National Biomarker Development Alliance; Marisa Dolled-Filhart, PhD, Merck; Thomas J. Flotte, MD, Mayo Clinic Cancer Center; Karen Hansen, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; Nadia

Haque, PhD, Genentech; Laura Lyman Rodriguez, PhD, National Human Genome Research Institute; Wendy Selig, WSCollaborative; and Alexa Sirko-Osadsa, PhD, FACMG, Novartis Institutes for BioMedical Research. This group and NCCN staff, including Robert Carlson, MD; Marian Birkeland, PhD; Jessica DeMartino, PhD; Lyn Fitzgerald, MJ; Patricia Goelz, MPH; Joan McClure, MS, and Diane Paul, MS, RN, convened in Philadelphia, PA, on March 30, 2015, to begin to identify and address the most critical concerns around tissue allocation that would help lead the discussion at the Policy Summit.

Summit Introduction

Robert W. Carlson, MD, Chief Executive Officer, NCCN, welcomed attendees and noted that the Summit would continue exploring issues identified by the Work Group, with an emphasis on the patient perspective.

Findings and Conclusions of NCCN Tissue Allocation Work Group

Work Group Co-Chair, Dr. Sullivan, identified many potential shared goals among the various stakeholders, who include individual researchers, their institutions, drug development and related companies, patients, and others. The shared goals include, but are not limited to: (1) recognition that the patient is the most important stakeholder in the process; (2) the need for high-quality tissue samples that can be used for diagnostic and research purposes; (3) standardization of collection and processing methods to ensure quality; and (4) clarification and simplification of sample sharing requirements. However, the Work Group also noted that competing needs related to the purpose for the tissue sample and the quantity required create impediments to reaching those shared goals.

The Work Group identified challenges facing the establishment of tissue allocation policies or procedures. These are briefly summarized in the following table.

CHALLENGE	EXPLANATION
Sample Quality	Inconsistent quality of tissue samples, largely attributable to non-standardized pre-analytic variables in tissue processing; requires determining who should set standards and what those standards should be
Documentation	Assurance that evidence-based quality standards are being followed and met; assignment of responsibility for documenting processes and procedures used
Tissue Quantity	Guidance on use of limited tissue samples, sample storage and management
Logistics	Understanding and standardizing the complex logistics needed throughout the complete cycle from tissue procurement through cost recovery

Data-sharing is another critical issue, according to the Work Group. Dr. Sullivan commented that the Oncology Research Information Exchange Network (ORIEN) project, in which Moffitt Cancer Center participates, requires that all data derived from ORIEN samples be available for use by all participants (with a few exceptions).

Dr. Sullivan then briefly detailed industry's interest in using tissue samples, which ranges from better understanding a disease process to researching drug responses to discovering biomarker associations with either efficacy or adverse events. As with academia, industry research is reviewed and approved by a scientific committee prior to implementation, and all subjects must provide informed consent. There are several "points of contention" between academia and industry in regard to tissue use, he explained. These include the physical form of the tissue to be shared (e.g., blocks vs. slides), the amount of tissue required for clinical trials, and whether there is a known use for the tissue when it is requested.

Dr. Sullivan concluded his presentation by noting that the Work Group identified more problems and concerns than it did possible solutions, but he hoped the further discussion during the policy summit would yield answers.

Ms. Carrithers followed with a presentation of the Work Group's deliberations around the IRB's role in tissue allocation. Institutional IRBs are responsible for ensuring compliance with all regulations, including informed consent, and they also review how tissue will be used internally or shared externally. She provided examples from several institutions of their biorepository rules and expectations. In regard to sharing tissue outside an institution, Ms. Carrithers noted that samples used to be shared much more

freely, but, due to recognition of their finite nature and the possibility for commercialization, sharing has become much more guarded. Most institutions use material transfer agreements (MTAs) when sharing tissue, with thousands issued every year. These govern the transfer of tissue and delineate the rights of the provider and recipient. In the past, MTAs were two-page documents written in standard language, signed by lower-level personnel. Today's MTAs are much longer and more complicated, require extensive negotiation, and must be approved by high level officials.

Ms. Carrithers continued by highlighting some prior and ongoing efforts to address issues related to tissue samples—specifically, how to ensure uniformity across biorepositories. For example, in 2009, the NCI's Office of Biorepositories and Biospecimen Research developed key principles for national biobanks that included, among others, the need for standardized collection and distribution procedures, standardized data sets, and standardized consent and MTA documents. The NCI Cooperative Human Tissue Network has developed a three-tier priority system for allocating tissue to investigators on a rotating basis. She pointed out that tissue transfer is not cost-neutral and requestors must recognize and be prepared to assume the responsibilities and costs associated with tissue procurement.

Ms. Carrithers closed her presentation by echoing some of the challenges to tissue allocation previously mentioned by Dr. Sullivan. Of key importance: (1) variability in collection, processing and storage procedures; (2) differences in degree and type of annotation; (3) inconsistencies in scope and type of consent procedures; (4) differences in allocation policies and MTA requirements; and (5) wide variation in the quality of specimens and data.

The summit's moderator, Clifford Goodman, PhD, The Lewin Group, asked each of the presenters what was lost by not handling tissue allocation well. Dr. Sullivan offered that patients were not getting on trials fast enough, or were not getting on the right trials, and Ms. Carrithers noted that patients were losing out on potential benefits after putting themselves at risk.

The "Garbage-In" Problem in Cancer Testing

Kenneth Bloom, MD, President and CEO, Clarient Pathology Services, and Chief Medical Officer, GE Health, followed with a presentation focused on the downstream implications of non-standardized tissue procurement and handling techniques and how this is currently being addressed. He noted that he was speaking as a member of the National Biomarker Development Alliance (NBDA), a multi-

stakeholder alliance collaboratively creating the standards required for end-to-end, evidence-based biomarker development to advance precision (personalized) medicine.

Dr. Bloom noted that non-standardized techniques can lead to multiple problems in both the clinical and research arenas, including misdiagnoses, the inability to reproduce findings, and misidentification of biomarkers. He then shared examples of each situation. He also cited data indicating that 32%-75% of testing errors occur during the pre-analytic phase, and 60% of those are due to poor or insufficient tissue. Dr. Bloom acknowledged that some parameters cannot be standardized, but said that what can be, should be. This is particularly important because, in his opinion, true precision medicine cannot come to fruition unless biomarkers are "quantifiable, reproducible, and clinically relevant." Pre-analytic variability is responsible for much of the variation in biomarker testing.

The NBDA has identified five key elements to standardize, along with a suggested standard for each. The five elements are: (1) time to stabilization; (2) method of processing; (3) method of stabilization; (4) meta data collected; and (5) storage conditions. A Memorandum of Understanding between the NBDA and CAP is underway with the intent that CAP will adopt the recommended standards and make adherence to them a requirement for CAP accreditation. Dr. Bloom believes it will take two to three years for CAP to accept these standards, and then there will be "a long process to accreditation."

Academic Cancer Centers' Tissue Practices

Representatives from two NCCN Member Institutions then shared with attendees how their respective institutions deal with tissue collection, processing, and allocation. Dr. Flotte talked about Mayo Clinic Cancer Center's frozen section laboratory, which handles about 20,000 specimens annually that are generated in Mayo's 60 operating rooms; about 5,000 of them are intended for IRB-approved research activities. Mayo Clinic Cancer Center is unique in that the tumor of every patient undergoing surgery is preserved in a frozen sample. Highlights of the Mayo lab include:

- An understanding that the needs of the patient come first (a core value throughout Mayo)
- Commitment to training pathology and surgical residents and fellows
- Standardized processes from acquisition through allocation (e.g., standardized gross surgical pathology templates, 90 minute maximum time from patient to preservation)
- Each specimen is frozen in a custom-made microtome that sits adjacent to the lab pathologists

- The lab is laid out in a “golden triangle” where the pathologist, histotechnologist, and person grossing are in direct proximity to each other for the purpose of communication
- The specimen being examined under the microscope is projected on a large screen for all in attendance to witness in real time
- Because biomolecules (DNA, RNA, proteins) are subject to degradation, specimens are prepared as 3 mm cores
- No more than ¼ of a tumor sample is ever given away

Dr. Flotte provided some statistics regarding the Tissue Request Acquisition Group, or TRAG. In 2013, there were more than 6,000 requests for tissue samples at the Mayo Clinic, of which 73% were fulfilled. The top four reasons that requests could not be honored were: (1) all the tissue was needed for diagnosis; (2) the samples were benign; (3) the request was not consistent with the research protocol; and (4) there was no tissue of the type requested. He also provided information regarding the types of tissues collected and requested. Finally, Dr. Flotte briefly discussed the data systems and informatics needed to manage all the steps related to tissue acquisition, processing and allocation.

Veronique Neumeister, MD, Yale School of Medicine, then discussed Yale’s Pathology Tissue Services (YPTS), which is a “pathology-based central tissue resource lab providing comprehensive tissue related services and material for investigators at Yale and beyond.” She noted that the YPTS has four branches: including Developmental Histology, Tissue Procurement and Distribution (TPD), Clinical Trials Tissue Services, and Specialized Translational Services (of which she is the Director). Dr. Neumeister talked briefly about each section, describing its mission, how it is staffed, relevant scientific techniques and methods, and key statistics related to its operations.

The Developmental Histology division focuses on tissue microarray technologies and, in FY 2013, delivered 3,527 tissue microarray slides to researchers at Yale University and around the world. Microarrays are the preferred technique because they allow viewing of multiple cores on one slide, and also multi-fold redundancy owing to multiple cores of the same tumor. The TPD Facility is responsible for providing high quality annotated fresh and frozen tissue to researchers and writes Standard Operating Procedures for tissue collection and annotation for multiple cancer types. The Clinical Trial Tissue Services procures, prepares and submits tissue for clinical trials around the world. Finally, the Specialized Translational Services group provides Tissue-Based Assay development in the CLIA lab setting

and specializes in quantitative immunofluorescence analysis. Dr. Neumeister concluded by stating that all four branches use a cost recovery model that is applied to both internal and external users.

Diagnostic, Clinical, and Research Concerns Roundtable

The first roundtable, moderated by Dr. Goodman, examined a variety of concerns from the perspectives of key stakeholders, including investigators, clinicians, industry and patients. The panel included: Carlos Arteaga, MD, American Association for Cancer Research (AACR); Phil Branton, MD, College of American Pathologists (CAP); Jeffrey W. Clark, MD, Massachusetts General Hospital Cancer Center; Marisa Dolled-Filhart, PhD, Merck; Dr. Flotte; and Rosalyn Meyer, PhD, Yale University School of Medicine and cancer patient.

Dr. Goodman opened the roundtable with the same question posed to earlier speakers—namely, if tissue procurement and allocation is not being done right, what are the consequences? Dr. Meyer said that the possibility of tissue not being available in the future for confirmatory or other purposes will be a loss for patients and researchers; another is the possibility of a life-threatening misdiagnosis. Dr. Arteaga said there would be a loss in innovation, because low quality or insufficient tissue precludes more detailed or in-depth studies that could lead to better drug development. Dr. Branton commented that most cancer specimens come from community clinics and regional hospitals, where pathology support is often "less sophisticated." Dr. Flotte added that even if many of those samples are sent out for more advanced review, the lack of consistent pre-analytics makes it hard for them to be read and compared. Dr. Clark was concerned that poor tissue quality means that people cannot get on clinical trials that could benefit them and others. Dr. Dolled-Filhart concurred, noting that problems multiply when the trials are international in scope.

Dr. Goodman then asked panelists to consider why the problems have yet to be resolved, since they are not new. "Cost" was one response, with panelists commenting that additional resources would be needed to comply with some of the proposed standards. One example cited several times during the discussion was that to process tissue in a specified short time period (e.g., 60 or 90 minutes), technically skilled staff people must be dedicated to retrieving the tissue in the operating room, transferring it into fixative, and documenting the details of the process. In a large institution with multiple operating rooms in multiple locations in simultaneous use, it would be difficult to achieve this. Likewise, smaller institutions that already have limited pathology services would find it difficult to dedicate personnel for

these functions. Panelists also noted there are not yet adequate reimbursement codes for the level of work that would be required, although Dr. Clark thinks they will eventually be created. Another response was the lack of "cultural pressure" to push the standards forward. Dr. Branton believes that as pressure grows, so will the desire for standards and the willingness to reimburse for them.

The discussion then turned to reasons for insufficient tissue. Numerous causes were suggested, including shortage of patients, insufficient quantity and/or quality of a given specimen, and lack of willingness to share existing specimens.

The discussion then addressed tissue sample ownership. Dr. Flotte noted that, in the past, pathologists acted on the principle that patients owned their samples, but as legal and regulatory requirements grew, pathologists came to believe that they owned the tissue with intent to act in the patient's best interest. Dr. Branton pointed out that, in many cases, patients "sign away their rights" to tissue collected when they consent to surgery. The panelists concurred that patients are becoming more aware of tissue-related issues, and Dr. Arteaga noted that if patients and doctors have a relationship built on trust, patients are generally more than willing to donate extra tissue for research purposes. Finally, the panelists discussed the pros and cons of re-biopsying patients to obtain more tissue. In general, the discussants agreed that it should only be done in cases of medical necessity, leading Dr. Goodman to conclude that "there should be a high hurdle for second biopsies." Dr. Dolled-Filhart pointed out that even when medically necessary, second biopsies can be tricky because of heterogeneity issues with samples taken at different times.

Dr. Goodman closed the discussion by asking participants to name one critical breakthrough that could happen in the next five years to reduce the variability of samples and increase their quality. Dr. Arteaga said it would be nationwide biospecimen standards in response to patient demand, leading to increased quality of biomarker collections. Dr. Branton said it would be "more robust information technology, data capture, and storage to allow for analysis of meta data." Dr. Clarke agreed and suggested that the scope of data being collected on each patient would widen. Fewer barriers to clinical trial entry as a result of standardized collection was posited by Dr. Dolled-Filhart. Dr. Flotte hopes for CAP standards and metrics for pre-analytic data, and a recommendation that tissue will be acquired and processed in under one hour. Dr. Meyer suggested that, at the current pace of knowledge, it is hard to predict what we will know in five years, but the issues discussed today will likely still be relevant.

Regulatory, Policy, Ethical, and Patient Concerns Roundtable

The second roundtable and final session focused less on the scientific and technical aspects of tissue allocation and more on the patient perspective. This session was again moderated by Dr. Goodman, and included panelists Ms. Carrithers; Anitra Engebretson, Pancreatic Cancer Action Network; Hank Greely, JD, Stanford Law School; and Nadia Haque, PhD, Genentech.

Dr. Goodman began the discussion by asking if patients were being engaged in decisions around tissue allocation. Ms. Engebretson commented that she was happy with the summit's emphasis on patients, because patients do care about having access to their tissue and also about what happens to it later. She noted that informed consent was a big issue. Regarding informed consent, Ms. Carrithers noted that there is a lot of variability between institutions. Overall, there is a move to make informed consent documents more patient-centric by addressing literacy concerns and making them generally more readable, but she acknowledged that they remain too long and detailed. She believes a consent form should detail what could happen with the patient's excess tissue and who might have future access to it.

Mr. Greeley took a more cynical stance on informed consent, saying that studies have shown that "most subjects don't know the next day what they agreed to." He suggested that perhaps it might make more sense to think about patients giving "permission" rather than consent, since often no one really knows how excess tissue might be used in the future. So instead of giving consent for unknown future uses, patients would give general permission to use their tissues for research purposes, with perhaps some mechanism to keep them informed (e.g., newsletters). Dr. Haque said that Genentech is moving towards a more comprehensible informed consent document, but that since future uses are not always known, the language has to be broad. Genentech does not want to have to re-consent patients later, given how hard it can be to track and find former subjects. Ms. Carrithers said that, in her experience, most people want their tissue to be used "wisely and well" more than they want it used for a specific known purpose. She suggested the possibility of a form that includes both consent and permission—consent for the known uses and permission for the yet-unknown ones. Ms. Engebretson concurred, noting that a recent small survey of pancreatic cancer patients revealed that 100% would agree to give their excess tissue to research, and 57% said they would even give additional tissue for research if needed. Mr. Greely commented that informed consent evolved in response to clinical trials and was never really intended for future research endeavors.

Dr. Goodman then asked who really owns the tissue once it is taken from the patient–Is it the pathologists who study the tissue? The patient who gave it? The final recipient of the tissue? Mr. Greeley pointed out that there is no absolute answer, as the issue of ownership is usually defined through agreements between involved parties. Ms. Carrithers said that, at Johns Hopkins University, if the question is not directly addressed in the MTA, it is then considered the owner. Ms. Engebretson said that patients think it is theirs and that they should have access for future testing or any purpose that could benefit them.

In response to a question regarding ownership of the intellectual property that arises from use of the tissue, Mr. Greeley said that, again, it is owned by whomever it was assigned to as part of the agreement. Unlike physical property, intellectual property must be assigned to a person, not an entity, although the person can assign it to an entity later.

The group then briefly discussed if patients should be told that their tissue could generate profit for its users. Dr. Haque said that would be difficult to do at Genentech, because they receive deidentified data; Ms. Engebretson noted, however, that she has seen such consideration and language in a consent form.

Data-sharing and partnerships were addressed next. Dr. Haque said that partnering is generally driven by need. Ms. Carrithers commented that Johns Hopkins University has numerous partnerships, many of which include data-sharing requirements. The panelists noted that two current policy initiatives—21st Century Cures and The President's Precision Medicine Initiative—explicitly require data-sharing practices.

Dr. Goodman asked audience members about the greatest unaddressed concerns of patients. One respondent—a scientist and cancer survivor—commented that patients want to know where their tissue will go and if there will be any left if they need it later. They do not really care about who "owns" the tissue, as long as they have the opportunity to direct how it gets used. Another commented that the barriers to clinical trial participation need to be simplified.

Dr. Goodman closed the session by asking each panelist to name one thing that can be done to engage patients in this issue that will benefit them, other stakeholders, and biomedical science overall. Ms. Engebretson said it would be to initiate dialogue between patients, doctors, and investigators, but also

to ensure that everyone involved will be “responsible stewards” of the patients’ tissues. Dr. Haque contributed “education and awareness.” Ms. Carrithers pointed out that the PCORI initiatives have fundamentally changed the research landscape and provided opportunities for patients to better understand and participate in the research process. Mr. Greeley said people with cancer are likely to want to help advance the science, but that it will be harder to engage non-patients because “they don’t have a dog in the fight.” He suggested appealing to the “information altruists” in healthy volunteers.

Dr. Carlson thanked Dr. Goodman and all the panelists for their participation.