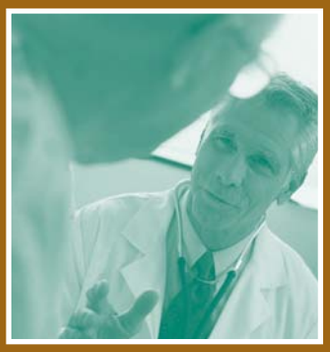
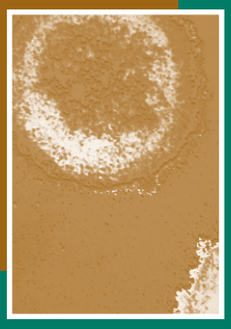
MODULE

6





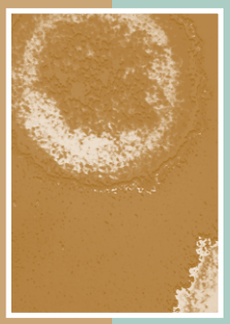
Cancer Research: A Guide to Clinical Trials

Tissue and Its Use

A SELF-STUDY GUIDE FOR
PATIENT ADVOCATES

COALITION
OF NATIONAL CANCER COOPERATIVE GROUPS, INC.
SAVING LIVES... ADVANCING SCIENCE... THROUGH CLINICAL RESEARCH

The Coalition of National Cancer Cooperative Groups



The Coalition of National Cancer Cooperative Groups, Inc. (the Coalition) was formed in 1997 by the foundations associated with seven of the National Cancer Institute's (NCI) Cooperative Groups. Over the last 25 years, Cooperative Group studies have been responsible for many of the major discoveries in cancer treatment.

The Coalition of National Cancer Cooperative Groups is an organization dedicated to improving the quality of life and survival of cancer patients by increasing participation in cancer clinical trials. Through a variety of programs, activities and services, the Coalition works to improve awareness about cancer clinical trials and to develop and manage new trials. Members of the Coalition include cooperative groups, patient advocate organizations, and cancer research and treatment centers. The Coalition works toward this goal through programs, activities, and services developed for our members and partners, including:

- *Cooperative Group Patient Advocate Training*
- *Patient Advocacy Program*
- *Summit Series on Cancer Clinical Trials*
- *National Awareness Campaign*
- *Web-based Applications, such as TrialCheck®*
- *Cancer Trials Support Unit (CTSU)*
- *Public Policy Initiatives*
- *Alpha Oncology, Inc.*

For information on these programs, contact Nancy Powell Connelly, Director of Communication, 1-877-520-4457.

COALITION
OF NATIONAL CANCER COOPERATIVE GROUPS, INC.
SAVING LIVES... ADVANCING SCIENCE... THROUGH CLINICAL RESEARCH

TO: Cancer Patient Advocates in Cooperative Groups

It is VERY IMPORTANT to:

- Read this and answer the "Thought Provoker" questions BEFORE attending the workshop!
- Read The Advocate Role: Cooperative Groups handout carefully.
- Bring this Self-Study Guide and all handouts WITH you to the workshop.

Welcome to the Coalition of National Cancer Cooperative Groups, Inc. Training Program. This program was created by cancer patient advocates who are members of the Coalition's Patient Advisory Board (PAB) and by an additional planning team of experienced educators and advocates representing several kinds of cancer. It is designed to give you specific information that can be used immediately in your committee meetings and other contacts with your Cooperative Groups. All currently planned modules are listed in *Appendix B: Training Program.*

Each module includes:

1. A Self-Study Guide
2. An Interactive Workshop
3. Web-based curriculum for self-study

In addition to the modules, an *Advocate's Handbook* is available that houses a glossary, the "Advocate Role" handouts and "Thought Provoker" questions from each module, as well as additional tools to help apply your knowledge into your Cooperative Group.

Module 6: Tissues and Its Use (Self-Study Guide)

This guide discusses how tissue is handled through the NCI funded Cooperative Group System. When you have completed all of Module 6, you will have:

- Reviewed how tissue goes from a person into use for research
- Learned how Cooperative Groups create trials that use tissue
- Reviewed where advocates can play a role and highlight patient issues
- Become familiar with issues you are likely to encounter as patient advocates in cooperative groups

Thank you for your interest in helping make Cooperative Groups work better for the patients they serve.

Best regards,

Robert L. Comis, MD
President
Coalition of National Cancer Cooperative Groups, Inc.

ACKNOWLEDGEMENTS

A special thank you to our Coalition's **Patient Advisory Board** for presenting the initial idea and helping to develop the curriculum for each module.

Patient Advisory Board members for 2002 include:

- Deborah Collyar, Chair
- Wayland Eppard
- Pat Halpin-Murphy
- Michael Katz
- Hank Porterfield
- John Mussman
- Barbara Parker
- Susan Scherr
- Mary Lou Smith

For Module 6:

- *A hearty thank you to **Roger Aamodt, PhD**, NCI; **Marianne Bledsoe, PhD**, NCI; **Carolyn Compton, MD**, Chair of the Cancer Committee, College of American Pathologists; **Scott Jewell, PhD**, Director, CALGB Pathology Coordinating Office; **Michael Pins, MD**, Director, ECOG Pathology Coordinating Office; **Mark Watson, MD, PhD**, Director, ACOSOG Central Specimen Bank for sharing information and feedback.*
- *Advocate reviewers participating as a focus group included: **Paula Kim**, **Pam McAllister**, **Barbara Parker**, **Bambi Schwartz**, and **John L. Willey**. Thank you for your valuable input and providing the patient's perspective.*
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The development of this module was made possible by the Coalition's funders who financially support Coalition programs.

Thank you ALL very much!!

TABLE OF CONTENTS

How to Use This Self-Study Guide

The Self-Study Guide gives a quick overview of each subject, and focuses on discussions that are important as you participate in the Cooperative Group process. Please review it carefully before attending the interactive workshop, since it builds on these ideas, and answer the questions at the end of each chapter.

To New Patient Advocates:
You may want to start with *The Advocate Role* and accompanying *Advocate Role* handout section before delving into each chapter.

To Experienced Patient Advocates:
You may choose to skim the information and focus on sections that are unfamiliar to you. Think of the Self-Study Guide as a useful reference tool.

Tone

The Self-Study Guide uses a conversational tone with short descriptions rather than extensive textbook explanations. While the style is informal, the content is not. Much research has gone into each module.

The "Advocate Point"

The Self-Study Guide uses a special bullet to highlight ideas, issues, notes, and roles that are important to help you apply the information throughout the Cooperative Group system as a cancer patient advocate.

The "Info Bullet"

The Self-Study Guide also contains information bullets to offer additional insights on specific topics. You will find these located in the margins.

Bring the Self-Study Guide with your answered "Thought Provoker" questions to the workshop!

Thought Provokers

These questions help you summarize each chapter and think about how you might use the information to help improve the process.

Resources

There are many good resources that describe the various roles and processes in the clinical trial system. If you would like more detailed information, please see the listings in *Appendix A: Resources/References.*

Glossary

Terms in bold can be found in the Glossary, included in the *Advocate's Handbook.* In Module 6, definitions are not given at the first occurrence in the text for some terms. These terms can be found in the glossary.

CHAPTER 1

TISSUE BASICS

Module 6 is intended to be used as a guide, not as a textbook. It can also serve as a reference for discussions regarding tissue. You may want to read the material in steps, and focus on the chapters that most fit your needs first. Here is a summary of the concepts you will find in Chapter 1:

- The kinds of tissue and specimens used in research
- Why tissue is important to medical care, and to research
- The roles patients, surgeons, pathologists, institutions, researchers, companies, and products play in better treatment, care, and prevention
- The way tissue is stored, along with an introduction on how tissue is used in Cooperative Groups
- Some federal requirements for tissue, and a list of some of the pathology-oriented professional organizations

What is Tissue?

The terms "specimen" and "tissue" are used interchangeably in many research discussions (including this module), although tissue is only one type of specimen.

- Tissue is used to describe a group of cells in the body that perform similar functions (e.g. muscle, liver, blood, etc.).
- Tissue is also a common term used to describe a kind of biological specimen which is a portion of a sample selected for examination or sample or a selected subset of a population; can be random or non-random). The human body is made of many cells that, when grouped together to perform a specific function, are called a "tissue."
- Specimens can be small samples of any bodily tissue, fluid, or other substance.

The definition of "tissue" and "specimen" often depends on the context. If you don't understand the use of the term – ask!

Analyzing specimens that come from a person can provide clues about his/her health.

Here are examples of specimens that have been used in cancer research:

Specimens Used in Cancer Research

- Blood (plasma and serum)*
- Bone fragments
- Bone marrow
- Central nervous system fluid (brain and spinal fluid)
- Feces
- Hair
- Lung fluid
- Lymph fluid and nodes
- Lymphocytes
- Milk duct fluid
- Organ tissues (e.g. breast, colon, lung, etc.)
- Pancreatic fluid
- Peritoneal fluid
- Saliva
- Soft tissue
- Sperm
- Sputum
- Tears
- Teeth
- Toe and fingernails
- Tumor tissue
- Urine
- Vaginal fluid
- Excess normal tissue

Tissue use is evolving rapidly. Eventually, patients may be able to have their own tumor tissue tested to identify specific targeted therapy that will work on specific biological targets.

The world of tissue is immense, so we have limited Module 6 to primarily solid tumor cancers. We have attempted to include vignettes for **hematological** cancers along the way, but some of the procedures may differ.

Why is Tissue Important?

Tissue investigation allows us to learn how cancer cells work. It is critically important to most research efforts because there is an opportunity to learn more from existing specimens. When tied to **outcome** information (long-term results for participants in a study), new markers can distinguish sub-groups of patients that benefit from a particular therapy from those that don't. Tissue research creates the foundation for new scientific discoveries and therapies. Recent examples include:

- Learning about the biochemical nature of cancers, leading to the identification of new prognostic and predictive indicators (see chart below)
- Learning about the molecular and genetic basis of cancers to identify targets for potential intervention with agents that cause less damage to normal tissues
- Learning to identify more clearly the causes of cancers

> "New methods in molecular biology and genetics allow ever more information to be extracted from human biological material. The scientific value of such specimens continues to increase; in some cases, the tissue may have considerable commercial value as well."[1]
>
> — *T.H. Murray "Ethical Challenges in Research with Human Biological Materials"*

Can Tissue Change Clinical Practice?

Studies using tissue do not change clinical practice immediately, but may over time. Most studies involving tissue and some kind of marker must be verified by at least one additional research study before physicians will accept it as a true prognostic indicator or predictor of therapy.

Some characteristics, like Her2/neu (HER2), can be both a prognostic and predictive indicator. Tumors that overexpress the HER2 receptor are associated with reduced survival (prognostic). HER2 overexpression also predicts lower responsiveness to methotrexate-based treatment and tamoxifen, and higher responsiveness to doxirubicin-based regimens (predictive).

Key Terms in Cancer Care

	Definition	Example
Prognostic	• Indicates overall outcome: probability of living or dying of disease • Determines which patient populations are at greatest risk of recurrence and might benefit from specific therapies	• PSA in prostate cancer • Number of nodes involved • Epithelial growth factor receptor (EGFR) overexpression indicates poor outcome in nonsmall cell lung cancer (NSCLC), gastric, glioma, laryngeal, head and neck, and colon cancers[2]
Predictive	• Predicts likelihood of response to a specific treatment • Indicates which patients are more likely to respond to a particular treatment	• Loss of chromosome 1p predicts sensitivity to chemotherapy for oligodendrogliomas[3] (brain tumor)

The following example is something that has changed clinical practice, and is based on a study done in CALGB, and then verified by a SWOG study.

Since overexpression of HER2 has become a prognostic marker and a predictive marker, standardization of testing is critical. Physicians and patients have been confused about how to make treatment decisions based on HER2 overexpression. These dilemmas also apply to other cancers involving HER2, and serve as an excellent example of both the promise and the pitfalls of new biological approaches to therapy.

Example: HER2/neu and Breast Cancer Treatments

In order to determine why some patients did better than others in treatment trial C8541, CALGB performed a study to analyze three arms of the study. They found that women whose tumors were HER2 positive (HER2+), which accounts for approximately 30 percent of breast cancer, did better with the highest dose of AC (adriamycin/cytoxan) than those in the middle or lower dose arms.[5,6] These studies were verified by a SWOG study[7], and changed the treatment that HER2+ women are given, creating a new "standard therapy."

Unfortunately, these studies created an additional question – what was the most accurate measure of HER2 positivity? This unanswered question existed because two **assays** (lab tests) were developed, and each measured different things:

- Immunohistochemistry (IHC) - measures the amount of protein present (overexpression of the gene) in the cell. HER2+ is evaluated qualitatively by scoring a tissue as 0, 1+, 2+ or 3+.
- Fluorescence in situ hybridization (FISH) - measures gene amplification and gives a quantitative result without levels of positivity (either HER2+ or negative).

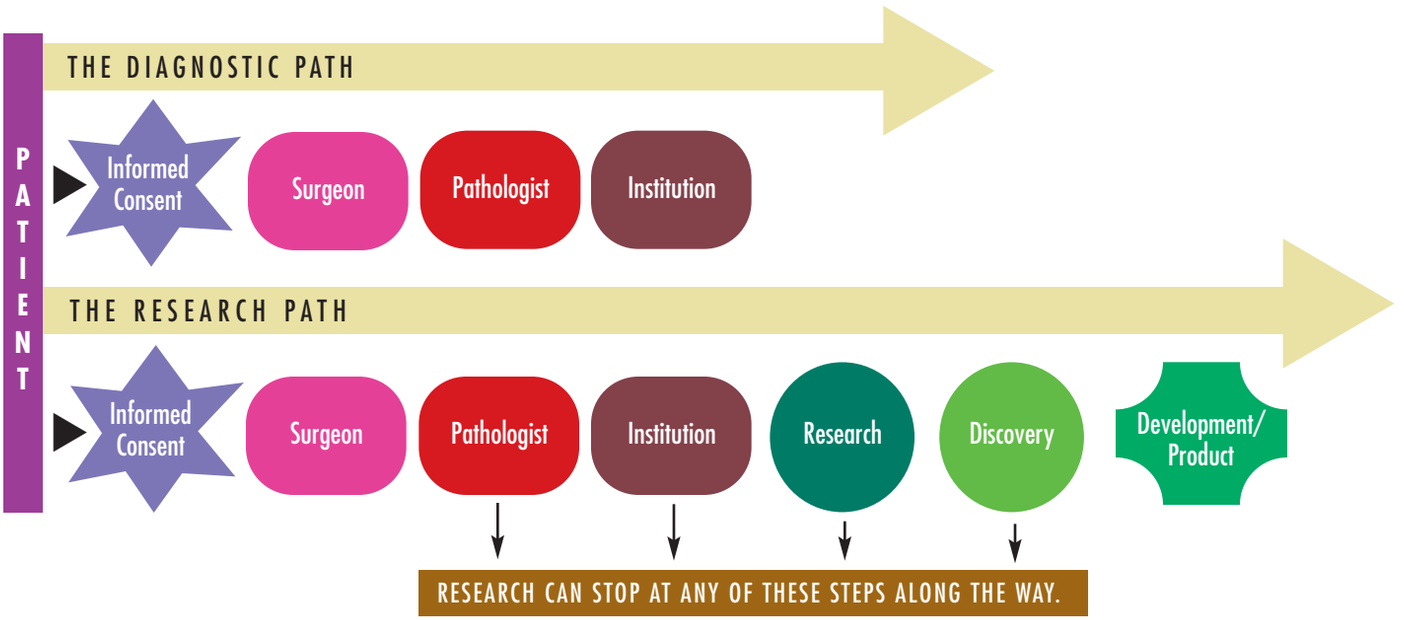
IHC was the first test available, and was considered "standard," but scoring is highly variable because of fixation, storage, reagents, and individual interpretation. FISH was developed later, and costs more.

In order to find out which one gave the most sensitive HER2 results, techniques were compared, and FISH is more sensitive than IHC. Agreement between the two techniques was also measured and found that, on average, they identified a similar percentage as HER2 positive.[8,9] The matter is still not settled everywhere, and some insurers will not pay for FISH due to its higher cost. A decision was made at the 2002 National Institute of Standards and Technology[10] to create a standard for HER2 kits.

Who is Involved in Tissue and Its Use?

While this might seem like a simple question, tissue involves many people who have a wide variety of reasons for its collection and use:

A Tissue's Path



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Patient advocates can help patients understand that giving tissue doesn't sacrifice their ability to use it for things like second opinions or future diagnoses. We can learn how tissue is used in research, what patient protections are in place, and help explain that to the patient and advocacy communities. It is important that each patient, however, choose what is best for herself or himself.

Patients

There are many steps involved with the collection, analysis, storage and ethical use of tissue. The first, and most important, step for an individual patient is the diagnosis. Many patients, however, do not know that a pathologist is the physician who determines or confirms the diagnosis of a suspected disease. Treatment for the patient is normally based on the initial tissue analysis.

Tissue donation is a similar concept to organ donation. Without patients who are willing to donate tissue for research, there will be no improvements in treatment, care or prevention. Patients often don't realize how important this step is.

Consenting for Tissue

Most people sign a consent form whenever a medical procedure is done. This kind of consent form is standard, and is required in order to allow a pathologist to look at tissue for diagnosis. Universities and research institutions that also provide care may include an additional consent form requesting the ability to use some of the excess tissue for research. This kind of consent applies to future research, with or without a specific clinical trial identified.

Consent forms vary greatly from one institution to another. Some include check boxes for patients to choose, while others are for general use (although these are much rarer today).

Surgeons

Surgeons serve a critical function in the initial process of tissue collection so that it can be used for diagnostic and research purposes. The surgeon determines which tissue, and how much is to be removed in the operating room or outpatient clinic, and has to remember if there are any special procedures that must be followed before it is transported to the pathology lab. These special procedures are used for some kinds of **biomedical** research (e.g. fresh/frozen tissue preparation, which is explained in Chapter 3). Some surgeons conduct clinical trials to analyze new techniques that lead to more specific treatment choices (e.g. sentinel node biopsies, tumor markers).

Pathologists

Pathology[11] studies traits, causes, and effects of disease that are seen in the **morphology**, (the form and structure of an organism or any of its parts[12]) and workings of the body. Since the genetic age, pathology has also extended to the level of molecular changes.

Pathologists are physicians who analyze tissue and specimens under a microscope or by other technology (e.g. DNA analysis, tumor markers, etc.) to study cellular changes. Pathologists play a key role in diagnosing disease, and in identifying and processing tissue that can be used in future research discoveries. They are generally the "keepers" of the tissue, assuring proper storage for additional diagnostic or research purposes.

There are many people who work in a pathology lab:

Pathology for diagnosis is ALWAYS the first priority. Only extra tissue that is not needed for diagnosis is used for research. There are also non-surgical procedures that collect specimens for diagnosis and research.

Pathology People and Functions	
Anatomic Pathologist	• Analyzes tissue (everything, except blood) that is removed from the body. Example: they evaluate **frozen sections** during surgery to identify cancer so additional surgical procedures may be performed if needed • Makes diagnoses and creates a pathology report • Includes forensic pathologists, who specialize in autopsies and medical legal issues
Clinical Pathologist	• Studies laboratory tests to diagnose and evaluate disease in **hematology**, microorganisms (bacteriology), chemistry, and immune systems
Laboratory Manager	• Supervises/coordinates laboratory functions, technical quality control, training, education, and technological updates
Pathology/Physician Assistant (PA)	• Reviews gross analysis and samples the larger specimen for processing in **histology**
Histotechnologist/ Histotechnician	• Prepares tissue for analysis, performs special stains and procedures
Medical Technologist/ Technician	• Performs and/or confirms blood test results and reports lab findings to clinical pathologists
Specialist in Cytotechnology/ Cytotechnologist	• Analyzes cells under a microscope; creates reports for normal cells; helps anatomical pathologist with report to identify the number of abnormal cells

This chart is meant as a reference, not to memorize. It is also important to note that a clinical pathologist does not mean the pathologist in a clinical setting – it is a technical term.

Pathologists practice in different settings, including:

- Community hospitals where they provide pathology services and educate community physicians
- Universities where they typically provide pathology services, teach residents and graduate students, and may conduct research on pathology methods and diseases
- Other settings such as independent laboratories that run medical tests, industry, and government

The majority of pathologists work in community hospitals. Beyond hospital practice, community pathologists may practice in private clinics, group practices and in other healthcare facilities.

Some pathologists pursue research, but this is usually only done in a university setting. Since most patients are seen in community hospitals, it becomes even more important to stress the value of research to various communities.

Training for Pathologists
Pathologists are required to go through four years of medical school, with an additional four to five years of residency training to be eligible to take board certification examinations. Many pathologists also undertake additional training in a subspecialty of pathology or as a research scientist, and obtain PhD degrees.

Institutions

Much of the work in a clinical pathology laboratory is completed by technical staff under the supervision of pathologists. The length of time that tissue is kept in a pathology lab varies by state law, and ranges from two to twenty years. After the required time period, pathology labs may throw tissue away. The patients may be able to obtain a release and avoid disposal, but most don't know that.

Tissue is housed in a tissue facility that is usually located in the same hospital or institution in which the surgery was performed. This tissue is considered the property of the institution once it leaves a person's body, and can be used or sold by that institution. Controversies surrounding these and other areas will be discussed in Chapters 4.

Be sure patients know that their tissue may not be available forever. If they want to keep it accessible for future testing, they may want to consider donating it to a research bank.

Research

Some tissue makes its way to be used in research for all kinds of purposes — this discussion is limited to cancer. In addition to pathologists, the main users of tissue are listed below.

- Basic scientists – laboratory based and do not treat patients.
- Clinicians – physicians who treat patients, conduct clinical trials, and perform laboratory-based research.
- Epidemiologists – scientists who study populations of people.

Many modern biomedical projects need different kinds of tissue than what has been traditionally collected and stored in **tissue banks** or **repositories**. Because of this, biomedical scientists are establishing more collaborative arrangements with oncologists, surgeons, and pathologists at teaching hospitals. This is often done on an ad-hoc basis.[13]

Studies in medical oncology, radiation oncology and surgery cannot be conducted without an adequate supply of tissue to determine the effect of the treatments.

Some clinicians conduct research that compares patients' tissue from different arms of a clinical trial after treatment to learn if certain tumor types respond better than others. Some studies use specimens to see if tumor cells respond to a particular therapy either during or shortly after treatment.

Tissue with clinical data/follow-up outcomes is critical because it can tell which treatments or approaches are effective for different types of patients. Cooperative Group tissue is extremely valuable for this reason. The medical community wants help from patient advocates in spreading the word about tissue with outcome data.

New Research Collaborations

The following box describes a unique research program, which is funded by NCI. Many investigators in the Cooperative Group system are part of a SPORE in their institution. The SPORE program has already begun to discuss future collaborations and clinical trials with some Cooperative Groups, especially regarding tissue collection and use:

The Specialized Program of Research Excellence (SPORE)[14]
In 1992, the NCI established SPOREs to promote interdisciplinary research and to speed the bi-directional exchange between basic and clinical science to move basic research findings from the laboratory to applied settings involving patients and populations. Each SPORE program focuses on a specific kind of cancer.

The goal of the SPORE program is to bring novel ideas to clinical care settings that have the potential to reduce cancer incidence and mortality, improve survival, and to improve the quality of life. Laboratory and clinical scientists work collaboratively to plan, design and implement research programs that have an impact on cancer prevention, detection, diagnosis, treatment and control.

To facilitate this research, each SPORE develops and maintains specialized resources, such as tissue banks, that benefit all scientists working on a specific cancer.

Companies

If research discoveries lead to a potential commercial use, a company is usually involved in order to turn it into a marketable product. It can take hundreds of millions of dollars to gain FDA approval on a device or an agent, and companies are currently the only ones who have access to those kinds of resources.

Commercial involvement is necessary to get new answers to patients. Patient advocates can play an important role in ensuring that patient interests are not overlooked in the quest for FDA approval.

Products

Products are created and approved through a series of steps that have been detailed in *Module 3: Drug Development* and *Module 4: Surgical and Radiation Therapies*. Tissue plays a critical role in this process, and two points have become very clear:[15]

- A great deal of work by multiple researchers, and samples from many individuals, rather than from any single individual, are needed to reach approval
- An individual study rarely leads to a commercial product

There are also many issues to resolve in the process of using tissue to develop products.

Tissue for Research

Most tissue that is used for research is collected in the same way as tissue that is used for diagnostic purposes. Samples of tissue are prepared for research using specific guidelines developed in a protocol. Pathology specialists in the treating hospital or an appropriate laboratory prepare specimens, and tissue is stored for future research use either in the original collection site or is sent to a central repository.

In some cancers, access to tumor tissue is very limited, which makes the development of tumor markers that can identify cancer cells in the body even more important.

The most valuable tissue is that which is processed, stored correctly, and attached to a database that includes clinical, epidemiologic and outcomes data from the patient. This type of processing allows researchers to look for patterns or identify new markers that may help predict, or even treat, cancer. Some of the reasons for this will be discussed in Chapter 2.

Tissue studies can lead to the kind of targeted or individual therapy that most patients want. That is why it is critical that patient advocates are involved in all discussions that learn about important new ties between therapy and biology.

Types of Tissue Storage

While tissue can be prepared by each institution, in Cooperative Groups, it is sometimes preferred to have a central location prepare all of the tissue in a consistent way. If the tissue is small, the entire piece is embedded in paraffin, which provides a solid mass that can be sliced into micron thick sections that can be penetrated by light for microscopic examination. The embedding procedure is automated; at a specified time, tissue is removed from the machine to be placed in fresh liquid paraffin, which is then solidified into a paraffin tissue block using cold temperatures.

Here is a brief review of the types of tissue storage:

Type of Storage	Description	Uses	Length of Time Usable
Formalin Fixed Paraffin Embedded	• Specimen is placed in a fixative solution known as formalin (buffered water with formaldehyde in it) to preserve the tissue before it degrades • Then placed in warm wax to preserve it indefinitely (embedded) • Prevents degradation, distortion, and contamination	• Can be sliced and put on a slide for microscopic review after it is stained • Can be sliced to extract DNA to look at genomic changes	• Indefinitely if stored properly
Fresh/Flash Frozen, Snap Freezing	• Specimen removed in surgery is processed very quickly • Either put directly into sub-zero temperature or put in compound that maintains cell morphology and then freeze at sub-zero temperatures	• Studies including genomic changes in m-RNA, DNA, and protein	• Indefinitely as long as sample is kept frozen for DNA, and below 700C for RNA and protein

The embedding procedure requires that all of the water in the cells be replaced by another substance. Analysis of m-RNA (messenger RNA) requires fresh/frozen tissue because it is very delicate and is often lost in fixed tissue.

The tissue is then stored in institutions, waiting to be used either for future diagnostic purposes or for research if the patient gave/gives their consent. The challenge is to get the correct tissue to the right researcher when it is required for study.

Tissue Banks

As stated above, **tissue banks**, otherwise known as repositories, house collections of tissue that are stored, recorded, and processed in similar ways. The most fundamental reason for developing a tissue bank is to provide appropriate specimens for research studies that vary from exploring basic concepts to applied investigations into the biology of a specific disease. The true challenge is how close the bank can come to the ideal preservation methodology and the complete description of the source.[16]

Additional NCI tissue resources can be found at http://resources.nci.nih.gov/ and at the NCI Cooperative Human Tissue Network at http://www.chtn.ims.nci.nih.gov/.

Input from patient advocates is needed in these discussions at the institutional level, as well as at the Cooperative Group level, so there is an understanding of the implications of selling tissue and the protections needed.

Tissue Use in Cooperative Groups

Tissue that is available for research purposes has to be prepared in a standard, careful way. Cooperative Group protocols have specific requirements for the way the tissue is handled, which adds to the value of including enough trial participants that have been consistently treated so conclusions may be drawn from studies. Some Cooperative Groups have established a central tissue bank within their Group, while others rely on a **virtual tissue bank** (tissue housed in different places, but is cataloged and available when needed).

Within Cooperative Groups, studies using tissue are included in virtually all committees. Some examples of tissue use include using specimens to:

- Identify better prognostic and predictive indicators
- Provide clues to identify subgroups within a cancer type, which can improve treatment or prognosis
- Improve our understanding of **pharmacology** of new agents for treatment, maintenance, or prevention such as: **pharmacokinetics,** and **pharmacodynamics**
- Identify new primary prevention strategies, as well as the prevention of additional cancers in survivors
- Create better early detection methods of primary or secondary cancers
- Control symptoms and side effects of treatment
- Improve Quality of Life (QOL) in areas other than side effects
- Further understand the basic mechanisms of disease. Examples: studies of **proliferation** in specimens collected during a clinical study
- Assess differences in the same disease among different patient populations and to provide information on the genetic basis of population-linked disease response. Many include determining a patient's **genotype** (specific genetic make-up) and **phenotype** (morphologic result of underlying genetic make-up)

For Instance:
A scientific study (CALGB 8869) analyzed a special receptor called HER2/neu in women with breast cancer who were enrolled in three different treatment arms of a clinical treatment trial (CALGB 8541). By knowing the outcome of treatment and studying the tissue from women in each of these arms, they were able to identify which women with HER2/neu over-expression survived longer (it was the highest dose treatment arm).[17,18]

Cooperative Group tissue banks are extremely valuable since they contain samples from patients who have been uniformly treated and followed for long periods of time.

As advocates, we can help make sure that pathologists have input in the design phase of Cooperative Group protocols to ensure useful collection and storage methods for each study. Advocates can also prompt pathologists in institutions to participate in Cooperative Group tissue requests to make sure answers to important correlative science questions are found.

Cooperative Group Tissue Banks

The clinical data that accompanies each sample sets Cooperative Group tissue banks apart from many other traditional collections. More tissue banks are striving to include clinical data, now that scientific techniques are able to link biological events with treatment outcomes.

Tissue banks can be located in one physical location, or in several. Most Cooperative Groups house specimens with different member institutions who have developed an expertise in storing a specific kind of specimen. Some Groups have as many as four separate locations to ship specimens for one clinical trial. Other Groups are attempting to centralize their operations.

Cooperative Groups face the challenge of managing tissue from many different institutions. Since many of the institutions are reluctant, or actually refuse to relinquish tissue to another entity for research purposes, the Cooperative Groups have devised creative ways to locate tissue in each institution, and work with them so that local pathologists can maintain control over the specimen.

Federal Requirements

When tissue is stored, it is subject to specific federal regulations. These regulations cover the basic requirements for tissue banks/repositories, but also leave a tremendous amount of room for interpretation, and are not always able to keep up with the pace of scientific discoveries. The regulations and agencies listed below are meant to give examples, rather than to provide an exhaustive list:

Examples of Federal Agency Requirements/Guidance Governing Tissue	
Office for Human Research Protections (OHRP, formerly Office for Protection From Research Risks (OPRR))[19,20]	• Repositories collect, store, and distribute human tissue materials for research purposes. Their activities involve three components: collectors of tissue samples; repository storage and data management center; and recipient investigators. • If supported (e.g. funded) by the Department of Health and Human Services (HHS), each component must satisfy certain regulatory requirements. Includes obtaining a Certificate of Confidentiality which protects privacy by allowing entities to refuse to disclose information to anyone outside the research project.[21,22] • Subject to oversight by an IRB • Uses general requirements for informed consent (45 CFR 46.116)[23] plus a clear description of repository operation, type of research to be conducted, conditions for releasing tissue and data, and procedures for protecting confidentiality • Supply collectors with an approved sample informed consent document
Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule [24,25]	• As of April 14, 2003, HIPAA requires patient authorization for release of Protected Health Information (PHI) (the few exceptions that exist use information without patient authorization for research, public health, and law enforcement). Specific conditions are listed for each type of potential exception. • Requirements include: limiting PHI without prior consent; giving patients new rights to view their own, and others, use of their medical records; restricting most disclosure of PHI to the minimum needed for each purpose[26] • Does not over-rule OHRP's Common Rule (45 CFR 46.116)[27] • Researchers may use PHI with proper patient authorization; forms can be combined with informed consent • Three types of waivers include: no more than minimal risk; research that could not be practically conducted without waiver; research that could not be practically conducted without PHI access and use
Food and Drug Administration (FDA) Regulations	• Uses general requirements for informed consent (45 CFR 46.116)[28] • Issued report to create a new regulatory system for human cellular and tissue-based products in 1997 with three main components: preventing contamination, establish "good tissue handling," and ensuring that clinical safety and effectiveness is demonstrated[29] • Regulatory requirements for cellular and tissue-based products span two centers at FDA (Center for Biologics Evaluation and Research[30] (CBER) and Center for Devices and Radiological Health[31] (CDRH) • FDA established the Tissue Reference Group (TRG)[32], composed of CBER and CDRH members to respond to inquiries from the cellular and tissue product industry • TRG identifies the need for further scientific or policy development, and interacts with the FDA Ombudsman's office on product designation requests.[33]

Federal regulations, while intended to protect patients and their privacy, have the potential to stifle research if not carefully applied. Additional resources for federal regulations are located in Appendix A, since this information becomes dated quickly.

Patient advocates can help make sure the scales are balanced between critically important protections for people who donate tissue, and for the scientific advances that we all want to see.

Professional Societies/Organizations

In addition to NCI, Cooperative Groups, and other organizations, professional societies play an important role in pathology by educating their members. Traditionally, each pathologist has had substantial leeway in determining how tissue and specimens from her/his lab will be used. Some pathology societies are now beginning to set standards and guidelines, although there is still resistance from some pathologists in this regard.

Patient advocates can help spur consistent use of patient tissues by engaging in an active dialogue with pathologists at all levels.

Here are some examples of pathology-oriented organizations, although this is not a comprehensive list. The following descriptions were taken from each group's Web site:

College of American Pathologists (CAP)
CAP serves and represents interests of patients, pathologists, and the public by fostering excellence in the practice of pathology and laboratory medicine. Publications include: *Archives of Pathology and Laboratory Medicine.*

American Society for Clinical Pathology (ASCP)
ASCP serves as a national resource for the enhancement of the quality of the practice of pathology and laboratory medicine. Publications include: *The American Journal of Clinical Pathology and Laboratory Medicine.*

American Society of Hematology (ASH)
ASH is concerned with the causes and treatment of blood disorders. Publications include: *Blood,* and *Hematology.*

Patient advocates have started to work with ASH because it is the professional organization for hematological cancers. Advocates do not necessarily have ongoing relationships with pathologists who belong to ASH, however.

For more information, see "Pathology Organizations" listed in Appendix A.

American Society of Cytopathology (ASC)

ASC is dedicated to the cytologic method of diagnostic pathology. Publications include: *The ASC Bulletin*, and a related journal *Cancer Cytopathology*.

Association for Molecular Pathology (AMP)

AMP was established to promote clinical practice, basic research, and education in molecular pathology. Publications include: *The Journal of Molecular Diagnostics.*

International Society for Biological and Environmental Repositories (ISBER)

ISBER focuses on providing information and education on tissue repositories and their issues, and on developing consensus standards. Publications include a quarterly newsletter.

Working with pathologists and their respective professional organizations is an untapped area for patient advocates. Many pathologists don't have much time to consider the importance of cancer research, and without input from us, they may not understand the importance of their contributions.

Notes

Thought Provokers for Chapter 1

These questions are designed to help you think about how to apply the information you have just read. Please use the other side if you need more space, and bring these to share at the upcoming workshop.

1. Why are pathologists so important in research involving tissue?

2. What do Cooperative Groups do with tissue?

3. What might be some of the reasons for donating tissue?

CHAPTER 2

FOLLOWING THE TISSUE

In Chapter 1, we briefly described the basics of tissue and its use. Chapter 2 will follow a solid tumor tissue through the process to learn how it actually works.

Tissue Starts With the Patient

Normally, a symptom or abnormal screening test prompts a person and/or their health care provider to delve into the medical system to find out what is the cause of the problem. This normally leads the person through:

- Screening tools to check health on a regular basis
- A series of diagnostic tests that try to locate the abnormality
- Some form of surgical procedure to go inside the body to get tissue, such as a bone biopsy
- A diagnosis given after a pathologist studies the tissue
- Further analyses for a malignant tumor (cancer) to classify it
- Treatment decisions based on the tumor's classification and extent

Some kind of surgical procedure is still necessary to remove and diagnose tissue for most solid tumors.

There are numerous kinds of tests that are used to find abnormalities, including blood tests, urine analyses, biopsies, aspirates, palpation, and various kinds of imaging scans. Once abnormalities are detected, specific tests are used to identify the type of tumor (e.g. mammogram, colonoscopy, lymphangiogram, etc.) which can be either benign or malignant.

Before a Procedure Takes Place

Before any tissue or specimen can be used for research, the patient must sign an informed consent form to release it for research purposes. This kind of consent can exist separately from the informed consent process for specific kinds of clinical trials. Details and issues about informed consents for tissue are discussed in Chapter 4.

Informed Consent for Research

Informed consent for tissue or specimens can be included in:

- A general surgical consent before an operation
- A separate consent form for research before an operation
- An optional checkbox in a treatment-oriented clinical trial consent form
- A separate consent form after an operation
- Any combination of above points

It is also important to ensure consent forms include all necessary information so that future contact (if additional consent is necessary) can be minimized, not only for researchers, but for patients as well.

Sometimes, the surgical pre-op staff is responsible for obtaining tissue consents, and they may not understand how important this request is for patients to consider. Once the patient has given consent, the procedure to collect the specimen is scheduled. Federal regulations apply to the use of tissue in research. See Chapter 4 for additional information.

Advocates can help raise awareness about the value of tissue, as well as the potential problems, so that each person in the process understands the issues. They can then help patients consider donating tissue with accurate and complete information.

A Specimen is Collected

The process used to collect and store tissue is sometimes called **tissue procurement**. If the specimen is removed by a surgical procedure (including bone marrow), the surgeon and nurse or technician work together to collect the tissue according to a pre-determined manner. The surgeon removes the suspicious mass. Sometimes, the tissue is taken to the surgical pathology gross laboratory during surgery for a **frozen section** (to see if cancer cells exist for example: when no preoperative diagnosis is available, to clarify an unexpected finding, or to determine the extent of the surgical dissection). Additional tissues may be removed for staging (i.e. lymph nodes). Generally, a nurse or technician places the tissue in containers of fixative, and labels them to take to pathology for processing.

If no surgical procedure is involved (i.e. blood or urine), collection is either scheduled if there are special procedures involved, or the specimen can be taken directly after consent. The timing of the informed consent can vary, as indicated in the following chart:

Times When Tissue Consent Can Be Acquired

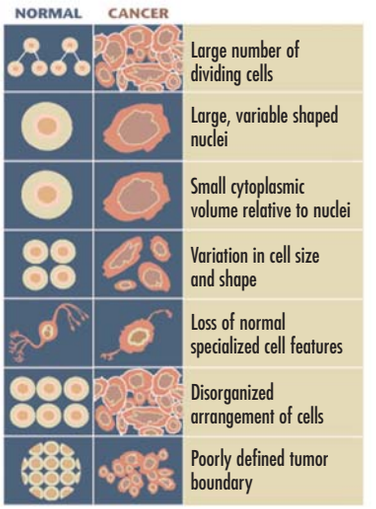
	Advantages	Disadvantages
Pre-Operative Visit	• Gives person time to consider giving tissue • More time available for explanation and questions	• Visit may be focused on other medical procedures • May feel intrusive if procedure doesn't involve diagnosis
Hospital Admission	• Convenient, if added to other hospital forms • Family members may be present to give input	• Adding tissue consent to other paperwork and procedures may be overwhelming • May be seen as intrusive during an emotional experience
At Surgery	• Can be included with surgical consent • Family members may be present to give input	• Anxiety prior to surgery is often high • Must be done before sedation is given
After Surgery	• Gives person time to consider giving tissue • Emotional stress has eased in most cases	• Can't take additional tissue • Physical condition may be worse • Person's focus may be on diagnosis or treatment

Knowing how the tissue will be used BEFORE performing a surgical procedure is critical. Why? Because certain experiments cannot be conducted unless the tissue is collected and stored in a certain way.

This is another reason that informed consent, and the issues surrounding it become critically important. Learning about, and considering a tissue donation just before surgery is sometimes too overwhelming for some, although many patients sign a consent form. Little is known about how much patients comprehend during this process.

Diagnosis First

If tissue is removed by surgical procedure (including marrow biopsies), it should be taken to pathology to render a diagnosis before it is prepared for research, or as **archival tissue**. Tissue is carefully divided into tissue **sections** while a **histological** (microscopoptic) examination is performed to look for changes that occur with cancer. These procedures are done to determine a diagnosis for the patient. Only residual tissue that remains after patient care is used for research, and any additional samples that are taken specifically for research purposes should be stated in the informed consent document that the patient signs.



Picture source:
http://rex.nci.nih.gov/behindthenews/uc/ucframe.htm

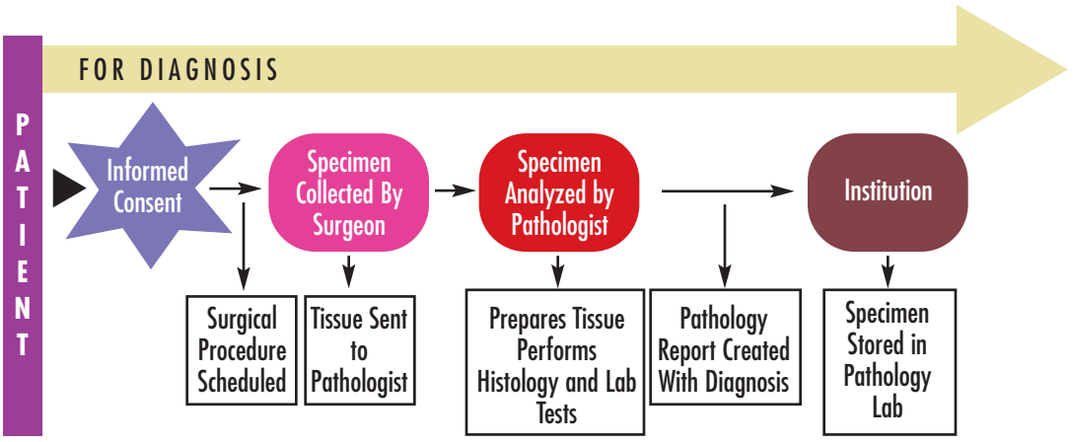
Microscopic Appearance of Cancer Cells[34]

Cancer tissue has a distinctive appearance under the microscope. Among the traits the doctor looks for are a large number of dividing cells, variation in nuclear size and shape, variation in cell size and shape, loss of specialized cell features, loss of normal tissue organization, and a poorly defined tumor boundary.

Research in Diagnostics

The NCI Cancer Diagnostics Program supports research to help to develop better diagnostic tools, including the development and support of human tissue banks that are essential to translational research. Tissues tied to patient outcome can be used to identify tumor cell characteristics including changes in DNA, RNA and proteins that can improve diagnosis as well as prognosis, treatment, prevention and other areas of research.[35]

Steps Involved in a Diagnosis



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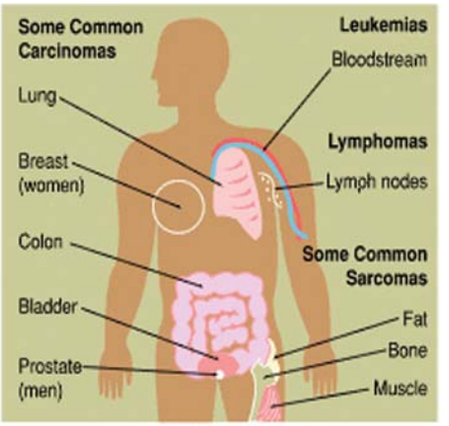
How Tumors are Identified and Classified

For more information, refer to the "Cancer Staging" section of the *Advocate Handbook*.

In order to characterize the extent of malignant disease that is present at diagnosis, staging techniques are used. The tumor type and tumor stage play important roles in determining the types of treatment choices a person may have.

The current classification system of tumor types was created long before the genetic age, from observations made by surgeons and oncologists as they studied how patient outcomes could be categorized by characteristics of a solid tumor. Here is a brief review:



Picture source:
http://rex.nci.nih.gov/behindthenews/uc/ucframe.htm

Solid Tumors

Most cancers are solid tumors that are identified by the organ and cell type of the original organ it was found in such as thyroid, colon, or breast. Tumors can also be identified by the types of cells found. These tumors may be:

Types of Solid Tumors	
Carcinoma	• Malignancy that originates from epithelial cells (cells that cover the surfaces of body structures [internal or external] or are derived from those surface cells) • Most common human malignancy: approximately 90 percent of cancers
Adenocarinoma	• Cancerous tumors of the gland • Most common type of carcinoma
Sarcoma	• Malignancies that arise from connective tissues including soft tissues and from hard tissues
Melanoma	• Arise from the pigment producing cells of the skin or other organs (e.g., the eye)
Glioma	• Cancers arising from the brain or spinal cord

The AJCC and UICC established the TNM system as the universal classification system to be used worldwide for solid tumors.

Most solid tumors (except for gliomas) are staged by the TNM system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), which is endorsed by numerous organizations including the National Cancer Institute. The TNM Atlas[36] system examines three separate aspects of the tumor:

- T evaluates the extent of the primary tumor itself
- N evaluates if, and to what extent, there is disease in the regional lymph nodes
- M denotes the presence or absence of distant metastasis (spread)

Lymphatic and Hematologic Tumors

Lymphatic and hematologic cancers are classified by cell type of origin, and are not staged using the TNM system. Historically, many histologic classification systems for these tumors have been used and some continue to be used. This has led to confusion, but there is progress toward standardization.

Diagnostics for hematological cancers can be more complex than for solid tumors.

Procedures for Hematologic Cancers
Symptoms may lead to a physical exam and a blood test. Pathologists then look at the cells through a microscope to see how they look and count the number of mature cells and **blasts** (immature blood cells) or lymph nodes. If cancer is found, a bone marrow **aspiration** or biopsy is performed to identify the type of cancer cells found in the blood. Additional tests may be ordered to determine the extent of disease.

General lymphatic and hematologic tumors include:

Types of Lymphatic and Hematologic Tumors[37]		
Leukemia	**Cell type of origin:** two types of white blood cells called: • lymphoid are lymphocytes, or white blood cells made up of T cells, and B cells • myeloid cells are white blood cells that give rise to blood monocytes, neutrophils, basophils, eosinophils, red blood cells, and megakaryocytes, which produce platelets	
	Acute	• Abnormal blasts cannot perform normal functions. Number of blasts increases rapidly, and disease gets worse quickly. • Includes: Acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML)
	Chronic	• Some blast cells present, but more mature and perform some normal functions. Number of blasts increases less rapidly, so people get worse gradually. • Includes: Chronic lymphocytic (CLL), and chronic myeloid (CML) leukemia
	Hairy Cell	• A rare type of chronic leukemia with abnormal white blood cells that appear to be covered with tiny hairs
Lymphoma	**Cell type of origin:** lymphatic system	
	Hodgkin Lymphoma	• Epstein-Barr virus may increase risk • Specific type of malignant cells (Reed-Sternberg) are found and may increase with disease
	Non-Hodgkin Lymphoma	• Cells in the lymphatic system become abnormal and can start almost anywhere in the body • Disease may involve a single lymph node, a group of lymph nodes, or in another organ and can spread anywhere in the body • Includes: Aggressive (intermediate and high-grade lymphomas which grow and spread quickly, cause severe symptoms) and Indolent (low-grade lymphomas, grow slowly; cause fewer symptoms)
Myeloma	**Cell type of origin:** specific types of lymphocyte called Plasma cells (white blood cells that produce antibodies)	
		• Unneeded, abnormal plasma cells that the body keeps producing; collect in bone marrow • Malignant plasma cells (myeloma cells) sometimes form a single mass, called plasmacytoma • Includes: Smouldering myeloma, solitary plasmacytoma of bone (SPB), and monoclonal gammopathy of unknown significance (MGUS)
	Multiple Myeloma	• Myeloma cells collect in many bones, can form many tumors and the antibodies they produce cause other problems
Myelodysplastic Syndromes	**Cell type of origin:** blood cells in bone marrow	
		• Often called pre-leukemia or "smoldering" leukemia. • Bone marrow does not function normally and not enough normal blood cells are made • Can develop acute myeloid leukemia (AML) • Includes: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia

In 2001, the World Health Organization (WHO) proposed a standard classification of hematologic and lymphoid neoplasms (tumors) that defines each using morphology, **immunophenotype**, genetic features, the proposed normal counterpart, and clinical features to arrive at a diagnosis.[38]

This classification system:
- Is the first classification of hematolymphoid neoplasia to receive worldwide acceptance, and serves as a roadmap for areas to study
- Emphasizes a multi-parameter approach
- Uses clinical features as a major part in the sub-classification of some tumors

Once the identification of the type of hematologic cancer is determined, it is staged by criteria that vary widely from one institution to another. Far less agreement exists in the method of identification of the malignancy and in the staging system, compared to solid tumors. In general, the histologic type and grade are stronger determinants of outcome (and response to therapy) for hematologic malignancies than is stage.

Tumor Grading[39]

Microscopic examination also provides information regarding the likely behavior of a tumor and its responsiveness to treatment for some cancers. Cancer cells with abnormal appearance and large numbers of dividing cells tend to grow quickly, spread to other organs more frequently, and are less responsive to therapy. Pathologists assign a numerical "grade," based on the **ploidy** and **s phase fraction** (estimates how fast a tumor is growing). A low number grade (I or II) refers to cancers with fewer cell abnormalities, and are normally called well **differentiated**. Those with higher numbers (III, IV) are sometimes called poorly differentiated.

For more information on staging cancer, see "Stages of Cancer" by Pam McAllister, PhD in your *Advocate Handbook.*

In addition to tumor grading, other tests are usually done (e.g. immunohistochemistry or fluorescence in-situ-hybridization (FISH), detailed in Chapter 3) to determine the tumor stage or classification. The stage or classification of the tumor is used to help determine the course of treatment for a patient.

The Pathology Report

After performing multiple steps, a pathologist prepares a report. The pathology report is one of the tools used in diagnosis, staging, prognosis and/or treatment planning. Surgical reports, other diagnostic tests, or scans are also important.

Pathology Reports Include

- Identifying information of the patient such as name, date of birth, medical record number
- Name of the surgeon providing the tissues or other material for examination
- A list of the specimens submitted for examination
- A gross examination, the physical appearance of the tissue as seen with the naked eye, of each specimen and its disposition (e.g. how tissue was submitted: in whole or in sections). Includes a brief description of size, color and other physical observations, with diagrams occasionally.
- A diagnosis from a frozen section (if done), including the tumor type and cell type of origin, tumor size, and tumor grade
- A diagnosis based on microscopic evaluation, and any significant observations. Includes an absence or presence of malignancy at surgical margins, type of cancer found, and any special tests done based on types of tumor (e.g. tumor markers)
- Comments from the pathologist
- The pathologist's signature

Patient advocates should be familiar with these reports, and encourage patients to obtain copies of them. Advocates should also encourage patients to ask their physicians to explain the reports. Because these reports usually rely upon the interpretation of a single pathologist, more patients should know that a pathology second-opinion may be important when uncertainty in a diagnosis exists.

Go to Appendix A for additional information on how to read a pathology report.

Follow-Up

Pathologists are required by law and for good medical practices to retain formalin-fixed, paraffin-embedded tissue specimens for years so they can be used for additional diagnostic purposes, if needed. Additional tissue analysis from the original **tissue block** (paraffin block containing the fixed tissue) may be needed if a recurrence or metastatic cancer is diagnosed.

Because tissue is used primarily for patient diagnosis and care, the amount of tissue available for research may be limited.

Pathological tests may also be run during treatment to see if any identified tumor markers have decreased, or to look for other prognostic factors. These are especially important in Cooperative Group studies that are analyzing response to treatment.

When Tissue is Collected for a Treatment-Related Clinical Trial

An informed consent form for analyzing tissue may be signed either before or after the surgical procedure. The consent form includes a clear description of tissue use for the trial and whether it will be used for future use. The patient may have the opportunity to reject either by checking yes/no boxes. The permission that a patient signs includes permission independently for:

- The sample to be stored and used for future research of cancer
- The sample to be stored and used for research to learn, prevent, or treat other health problems besides cancer
- The sample to be released to outside researchers, with an explanation of how outside researchers can obtain specimens

Clinical trials that use tissue can be handled in three different ways:

Ways Tissue is Used in Cooperative Group Clinical Trials

Timing	Collection Type	Relation to Study
• Written into the original treatment protocol	• Prospective samples • Sometimes collected before a specific scientific study for tissue has been defined	• Integral to the successful conduct of the primary clinical trial
• A companion/ancillary study can be written to accompany a treatment protocol with a separate consent form	• Prospective samples • Includes a specific scientific study at the time of primary clinical trial	• Independent of the primary clinical trial
• A separate tissue study	• Retrospective samples • Requires an additional informed consent process	• No other accompanying clinical protocol

Tissue consents are an area where patient advocates can help their own Cooperative Group and help create consistency between the Groups as well.

Tissue is Sent to a Cooperative Group

A Cooperative Group member institution sends tissue that is specified in a protocol to the Pathology Coordinating Office (PCO). An investigator who has an approved study through the Cooperative Group will then receive tissue for his/her study. Remaining tissue is banked for future research either at the PCO or by the original pathology department.

The following example has been supplied by CALGB, one of the first Cooperative Groups to start an organized approach to collecting tissue for correlative science studies:

Conducting Scientific Studies Requires:[40]

- A coordinated system that includes the centralized collection of tumor cells and tissues
- Storage under controlled conditions
- A comprehensive inventory
- A process to distribute specimens to investigators and to receive the assay results from research laboratories
- Policies to address responsible research, including safeguarding patient confidentiality

A tissue block has a limited amount of tissue, and eventually, a specific tissue will be used up and cannot be replaced. This is why some institutions retain control of their own samples. Some Cooperative Group PCOs have developed safeguards to prevent using the entire research specimen to convince institutions to provide the material necessary for the patient-consented clinical trial research.

Not all member institutions will release their tissue for use in Cooperative Group studies. This can prolong the answers to research question that need consistently treated patients and their outcomes.

Sometimes, tissue is not sent to a Cooperative Group even though the patient signed a consent form. One activity that patient advocates in Cooperative Groups could work on is finding out why (including legal and ethical reasons) some member institutions won't send tissue, and help resolve the issues so that answers can be discovered more quickly for patients.

Issues exist when the Cooperative Group cannot access the tissue in a way that allows them to perform important quality control tests.

For Example: NCCTG N9831[41]

The Intergroup (an NCI mechanism that allows more than one Cooperative Group to participate in a study for a specific cancer) clinical trial N9831 (sponsored by NCCTG) involves women with node positive, HER2 positive (HER2+) breast cancer. Researchers are studying different treatment options to see which one works best for women with HER2+ tumors:

- Testing for the presence of over-expression or amplification of the HER2 gene is critical
- Testing is necessary to ensure the success of the study, and that women receiving treatment on this study are eligible
- Results of HER2 testing of the first 119 patients enrolled in the study were analyzed to determine the accuracy of testing done by local as compared to central laboratories
- Concordance between the two tests for HER2 done in local labs was 74 percent, and 92 percent for central labs

These findings have led to a protocol amendment, which requires that all testing be done at the central lab for consistency and increased accuracy.

Patient advocates in Cooperative Groups may be able to help identify, and possibly alleviate, some of the issues and extra steps that Cooperative Groups must enact in order to appease some pathology departments and institutions.

Cooperative Groups have different procedures for collecting and handling samples.

The PCO and Its Role

Paraffin blocks are sent to the Pathology Coordinating Office (PCO) for processing by most Cooperative Group institutions. These blocks have been processed by the original pathology department, as described previously.

The PCO plays a very important role for its Cooperative Group. Procedures vary widely for each Cooperative Group, and even for each study. Each protocol states the procedures it will use. The following chart outlines some ways a PCO may operate:

PCO Role in Its Cooperative Group[42]	
Tissue Verification	• All paraffin blocks and slides are catalogued and matched to reports to ensure the correct tissue was submitted
Quality Control	• Vacuum pack and store to preserve cell components • Prepare Hematoxylin and Eosin (H&E) staining (see Chapter 3) and central review to check for diagnostic stage and quantity
Preparation for Studies	• Cut sections from blocks; prepare slides and send to investigator • If institution sent slides, process and send to investigator
Central Bank	• H&E sections and at least two unstained sections are filed in the event of need • Unused portions of blocks and slides are maintained at the PCO; blocks can be returned to submitting institution if needed • Specimens kept indefinitely unless patient withdraws consent. Tissue is then withdrawn from bank and returned to original source or destroyed • Special provisions for institutions that will not allow long term storage of blocks or will not release blocks • Other banks may store additional specimens (e.g. plasma, urine) during the study, and then relocate to the PCO • After a study is completed, tissues are sent back to PCO
Other Banks	• PCO and Data Management Center keep track of additional banks that may be held by an investigator. If that investigator leaves the Cooperative Group, the tissue must be turned over to a new Group designee
Policies and Procedures	• PCO maintains updated policies and procedures developed in their Cooperative Group to protect medical and legal concerns of the Cooperative Group, submitting institutions, and patients

Oversight for the use of tissue stored in the PCO, or repository, rests with the Cooperative Group's scientific committee and the Group Chair. The Lab Science Committee should review the proposed new use for the tissue, evaluate the scientific merit of that use, and consider its potential risk or benefit to the patient. After such an evaluation, the IRB that oversees the PCO determines the potential risk and whether or not to waive the need for additional patient consent. It is the responsibility of the local ethics review board or IRB to monitor the activities of the recipient investigator.

The "Anonymous" classification does not allow follow-up data that could identify better treatments by patient sub-groups. It also means there is no way to give a person the results of a genetic test done in research studies.

Type of Samples Regarding Privacy[43]	
Identified	• Readily linked to a particular individual, usually named or has other identifiers (e.g. date of birth, address) • In small sets of data, even information such as a postcode may be an identifier
Coded or Potentially Identifiable	• Material has identifiers removed and replaced by a code. • It is possible to use the code to identify the person to whom the data relate so that the process is reversible • Re-identifying would only be done in extreme cases (e.g. discovering harm to patient, etc.)
Anonymous or "De-Identified"	• Identifiers removed permanently or the tissue has never been identified • Cannot reverse the process and find out identity

Patient advocates can work toward informed consents that ask patients whether they want tissue used to be identified, coded or anonymous. Participants should also have the right to determine whether they wish to be re-contacted or not. Some patients get very anxious, while others want to give additional information.

While there are some guidelines in how to produce a tissue-oriented consent form, there are no standards yet.

Intergroup Specimen Banking Committee

This committee was created in 1998, and has worked to resolve issues involved in collecting tissue from many different sources for Cooperative Group research. They developed guidelines for collection, storage and distribution of patient specimens from Intergroup trials that each Group uses to form a minimum standard to promote and scientifically validate correlative science research from the Cooperative Groups.[44]

Steps Used with Tissue in Cooperative Groups

Each investigator who wants to use tissue from a Cooperative Group tissue bank follows steps like the ones listed below:

- Reads the Cooperative Group's policies and procedures on tissue use, and in writing to adhere to them. This includes obtaining a **certificate of confidentiality**[45] for any samples that have identifiable information for genetic studies. There are also several agreements that must be signed, including a conflict of interest form
- Submits an application to the appropriate Group committee(s) (e.g. laboratory/correlative science, etc.), requesting the use of tissue, along with a concept proposal that will undergo scientific peer review
- Presents proposal to the appropriate committee(s) and adapts it based on feedback received
- Gains approval from the Group's executive committee, and from Cancer Therapy Evaluation Program (CTEP)
- Secures funding for the proposal (this is normally independent of Group funding)
- Presents to the Intergroup (if necessary to obtain sample size)
- Obtains IRB approval
- Conducts the scientific study, and returns unused specimens within 60 days of completion
- Writes a manuscript, and submits it for publication

Protocol Specifics

The protocol specifies the type of tissue needed, the amount, where they are to be sent, and how samples will be used to answer a specific scientific question. Any unused tissues must be returned to the PCO. IRB approval is needed for all studies and patient identity must remain confidential. In addition, the investigator must also specify how the findings will relate to an advance in knowledge that leads to improvement in treatment.

Removing patient identities from tissue BEFORE it is sent to investigators makes it much safer for patients to maintain their privacy. This is a major advantage that patient advocates can point out when discussing tissue with patients and patient organizations.

How Tissue Gets to an Investigator

Once the protocol has been written and approved, the appropriate tissues (and accompanying pathology reports) are retrieved from institutional pathology departments by the PCO. There, it is stored until enough samples are available for use.

The study chair then makes a request to PCO personnel to process the cases, which includes cutting the paraffin blocks. Once this has been completed unstained tissue sections are sent to the scientific investigators who have been recruited by the clinical trial study chair to perform specific research analysis.

Scientific studies are performed in the investigators' laboratories in a timely fashion, and the results are sent to the Data Management/Statistical Center of the Cooperative Group.

Statisticians analyze the data, and correlations with clinical outcomes are made. The statistical analyses are sent back to the investigators for interpretation, conclusions, and publication.

All investigators are encouraged to find their own sources of funding. This can be a challenge, since most of these studies are expensive to conduct.

Criteria have been established to ensure that the resource will only be used for clinical relevance, and investigators must agree to follow the policies before they receive tissue. Non-members may be able to use tissue as long as they have a Cooperative Group partner involved, are approved by the Cooperative Group review panel, and agree to established tissue use policies.

When There Isn't Enough Tissue

Cooperative Group clinical trials include large numbers of patients so that the findings are likely to be true. When tissue does not arrive from institutional pathology departments, the statistical power of the scientific study is weakened, and may compromise the validity of the research. In extreme cases, the study may be closed due to an insufficient amount of samples to answer the scientific question posed.

Unfortunately, the trend indicates fewer institutions submitting tissue blocks. This seems to be based more on pathology department policies rather than legal or institutional requirements.

The effect of missing tissue samples on the outcome of a study is why it is important for patient advocates to learn about tissue, and to make sure local institutions understand and participate by complying with requests for tissue.

Publishing Results

Once completed, the studies are frequently presented at a professional meeting, and all are supposed to be written up for publication. Studies using banked tissues must submit manuscripts to the Cooperative Group central office/headquarters prior to submission for publication or presentation.

The faster results get published, the faster new advances can become part of "standard therapy" for most patients. Please urge your committees to publish their data as soon as possible.

Policies specify authorship on publications of clinical trial results, with the study chair as primary author and the committee chair last. Accrual tables are used to decide which institutions receive institutional co-authorship in Cooperative Groups.

Thought Provokers for Chapter 2

These questions are designed to help you think about how to apply the information you have just read. Please use the other side if you need more space, and bring these to share at the upcoming workshop.

1. Why is tissue linked to patients on clinical trials so valuable?

2. After tissue is used for diagnosis, how is it prepared for research?

3. What are the different ways tissue can be acquired for clinical trials?

CHAPTER 3

WHEN SCIENCE AND ETHICS CONVERGE

Most scientists try to make sure they perform quality scientific studies that will help people and are conducted in an ethical manner. It is clear, however, that there are issues that exist with researchers and with bioethicists on how to responsibly handle tissue in a way that will not cause undue risk or harm to individuals. This stems from the fact that what is "ethical" is based on subjective judgments, not on clear facts.

As a patient advocate, you may encounter some resistance toward your involvement in the research process. The key is to help everyone understand that you are there to help make the process work better for everyone, including patients.

Tissues from the body have whole new meanings in the genetic/genomic age, and specimens in research can create ethical issues surrounding the use and possible misuse of this material for people and their families. Some issues that arise in research studies are included in this chapter.

How the Use of Tissue Could Harm People

Cooperative Group trials are using tissue more and more to analyze outcomes in the hopes of creating better tools that can be used to make better decisions. This also means, however, that more patients and their families shall weigh the pros and cons of allowing the information gathered from their tissue to be used in research. One risk of tissue use includes the way patients may be identified in research studies that use their tissue. Risk of identification depends on how the identity of the patient specimen is maintained.

It is very important to understand the difference between privacy and confidentiality. As you can see from the definitions, they are NOT interchangeable!

Some Research Definitions:

Privacy: refers to persons and to their interests in controlling access of others to themselves. In the research context, privacy refers to how investigators collect or access identifiable data from participants.[46]

Confidentiality: refers to identifiable data and relates to agreements between the participant and the investigator about how the participant's data will be handled and to whom it will be disclosed. It is an extension of the concept of privacy.[47]

Currently, the concern for harm may outweigh evidence of harm, but the threats in this chapter are real, and need to be understood and included when creating protections for research participants. While most scientists and advocates understand and believe in the value of research using information obtained from tissue, we all need to be aware of the possible harm that could come to the individual.

Harms is a technical term that is used to convey the consequences participants of research may suffer due to their participation. Specific evidence of individual harm due to the use of tissue has not been documented. At this point in time, the fear of harm is what must be dealt with. Harms can occur in: physical, psychological, social, economic, legal, or dignitary categories.[48] This chart lists some specific potential harms or privacy risks:

Potential Harms or Risk to Privacy	
Discrimination Regarding Health Insurance and Employment[49]	• There is no reliable data on the actual cases of discrimination based on genetic information • Some people may have been discriminated against simply because they have cancer or some other disease • Confusing issue: Is information from a genetic test or an analysis of tissue different than answering questions about family history?
Stigmatization[50]	• Closely related to discrimination; carries the suggestion of blame, taint or unwholesomeness • Self-stigmatization exists in many individuals who are diagnosed with cancer. This can result in additional psychosocial distress
Ascriptive (Group-Based) Identity[51]	• Identity based on group membership (e.g. African Americans, Ashkenazi Jews, etc.) • If a specific group is identified with a higher risk of certain cancers, group members could be stigmatized or discriminated against
Familial Conflict (Individual vs. Family Knowledge)[52]	• Difficult choices develop in this situation (e.g. If a patient wants to be tested for a genetic mutation, does he/she share the results with family members? What if some members want to know and others don't? • Legal and ethical debates[53] surrounding genetic testing: Conflict can arise for the genetic counselor due to the duty to protect the confidentiality of the individual and the duty to warn family member(s) of possible harm • Duty to warn exists only if the possible harm "is serious, imminent and likely; prevention or treatment is available; and where a health care professional in like circumstances would disclose."[54] For example: familial adenosis polyposis (FAP) can be found through a genetic test, and could help prevent an early onset of colon cancer for family members • Family members do not have rights to protected information. They can only obtain information if the individual who was tested agrees to release it to them • The individual must consider these questions when choosing to have a genetic test: Do I want to disclose the information? Am I influenced by family members who wish to know the results? What about any family members who don't want to know?
Use of Tissue for Purposes Objectionable to Donor[55]	• Many consent forms ask for permission to use tissue for future unspecified purposes. No one knows what those future purposes might be, including researchers • Tissue could be used for a purpose that the individual believes to be inherently wrong • If tissue is used for purposes that are religiously or philosophical objectionable to an individual, the individual may suffer from psychological harm

It is important to remember that harms happen to individuals, and are not normally brought to the public's attention.

Example of Ascriptive Identity:
Human Genome Diversity Project (HGD Project) is an effort by anthropologists, geneticists, doctors, linguists, and other scholars from around the world to document the genetic variation of the human species worldwide. The HGD Project collects information on human genome variation to help understand the genetic makeup of all of humanity, not just some of its parts. The information will also be used to learn about human biological history, the biological relationships among different human groups, and may be useful in understanding the causes of and determining the treatment of particular human diseases.[56] The HGD Project has developed guidelines for the collection of tissue samples from minority groups.[57]

Informed Consent for the Use of Tissue

Informed consent originally focused on protection against physical harm. Over time, it has evolved into protection against a broad range of nonphysical harms lumped under the heading "psychosocial." Most patients want to be assured that the maximum information is gained, and that ethical practices are in place for the use of that tissue. The informed consent process should safeguard against harms due to the use of an individual's tissue.

Different Consent Approaches

Patients are often given the following options and asked to consent to none, some or all of the choices available.

1. Consent to the use of their tissue in the specific clinical trial in which they are participating
2. Consent to the use of their tissue in other cancer related studies
3. Consent to the use of their tissue in other health related research
4. Consent to be re-contacted in regard to their tissue.

Many tissue consent forms now contain check boxes and/or write-ins for the donor to use to indicate her/his choice.

Researchers and clinicians have searched for appropriate ways to bring the consent process to tissue samples. Many times, this means that the tissue consent may be added to the standard informed consent form for all clinical trials.

In cases involving tissue consent, all of the standard consent form requirements apply, including the ability for the participant to withdraw from the study. If someone does not want their tissue available for research after signing an informed consent form, data that has been generated from the tissue can still be used, but the tissue itself should be either destroyed or returned to original institution for patient care purposes.

The Blanket Consent Issue

A blanket consent[58] gives permission to use a person's tissue without giving the details of the research, and is often used to obtain permission for future unspecified research. Blanket consents have increased as scientists realize the value of the future use of tissue due to rapid discoveries about the structure and function of cancer and normal cells, and new tests for biomarkers (e.g. HER2/neu) and other exciting approaches.

Pros	Cons[59]
• Can provide options for patients to let them determine specified uses • Allows tissue to be collected in consistent way (e.g. past tissue collection similar, etc.) • Allows research to continue without tracking down patients over time (which may not be physically possible), and keeps expenses at reasonable levels • Allows researchers to study older tissue with clinical data to determine the role of new markers and discoveries • The National Bioethics Advisory Commission accepted the validity of consent for future unspecified use of tissue[60]	• May not fulfill one of the requirements of informed consent, which is disclosure of the relevant risks and benefits of the procedure • Cannot inform patient of the relative risks and benefits of that use • May not offer effective protection against the various other possible harms that might result from uses of biological samples • Difficult to track in tissue banks • Possibly confusing or upsetting for patients during initial diagnosis process • Could be seen as a symbolic expression of respect for individual choice; a formality rather than true respect

IRBs are increasingly unwilling to allow researchers to ask for broad blanket consent, and are asking for the use of different signature blocks for different types of consent for tissue. As in all parts of science and ethics, some agree with the blanket consent approach and some don't.

In order to weigh in on this controversy, patient advocates need to delve into the issue and consider all factors before expressing their opinions. This is an example of a topic where unknowledgeable advocates can be swayed by scientific persuasion, instead of thoroughly understanding, and deciding upon a position that represents patients.

Archived Tissue Samples

There are thousands of existing samples stored in tissue banks that are not accompanied by consent. These samples can be extremely valuable to researchers, but also carry complicated issues surrounding the way to use them ethically. This raises the issue: "Should researchers go back to each patient and obtain consent?" Unfortunately, this is a very controversial issue that will not have an easy solution.

Patients whose tissue samples are associated with a specific Cooperative Group clinical trial, could be re-contacted and asked for consent for a longer period of time than with many other clinical trial sponsors.

A simple, but some feel impractical, way of addressing this issue is to go back to each patient and obtain consent. While re-contacting people is an option (and the Internet has made this more feasible), it comes with its own set of problems:

- Re-contacting individuals could potentially cause harm through emotional or psychological distress, and through family conflict (discussed above).

When samples are drawn from identifiable groups, one major question that needs to be considered is: "Should the group be asked for consent?"[61] This is particularly important when seeking tissue from underserved and ethnic populations who hold different beliefs concerning individual and community responsibilities. Here are some general points to consider when looking at possible group consent:

Pros	Cons
• Respect for non-Western values and beliefs • Avoid group-based harms • Recognition of different cultural structures	• What constitutes a group or culture? • There may be no clear leader or consensus within a group • Individuals may not be able to make their own decision

"Until public policy becomes clearer, conscientious researchers may have to resort to vaguely declaring in informed consent disclosure that "there are no present plans" to share the proceeds of resulting commercial products with the tissue source."[62]

— CH Harrison "Neither Moore Nor The Market: Alternative Models For Compensating Contributors Of Human Tissue"

Making Tissue Available to Others

Sources of tissue resources which researchers can access include:

- Tissue banks established by some patient advocacy groups
- Tissue that companies buy and sell (commercial entities)
- Tissue held in community hospitals or academic centers
- Federally-funded tissue networks
- Cooperative Group tissue banks

Some of these entities sell tissue, while others process it for a small fee to cover costs. Most of these groups do not threaten the Cooperative Group system, but it is good to know something about them because the issues they bring up can also be applied to any tissue bank, including the Cooperative Groups. We will only address commercial interests here.

Well-informed patients may be concerned with who controls future use of tissue, and whether anyone will profit monetarily from the use of their tissue. While there is nothing wrong with commercial pursuits (they actually make more options available for patients sometimes), each person has a right to decide how they feel about it. As patient advocates in Cooperative Groups, we can help make this information as clear as possible.

Companies

There are also many types of companies that sell tissue for profit to other companies and academic institutions. Most use tissue that is donated from a variety of sources, while a few pay donors for samples. Below are a few examples, but by no means exhausts the list:

Company	Serves	Process for obtaining samples
Ardais Corporation[63]	Clinically-based discovery programs	• Samples obtained from medical institutions, possibly governed by local IRB • Each institution collects its samples and obtains informed consents to the extent required by applicable laws, regulations, and ethical standards
DNA Sciences[64]	Those who want gene-based diagnostics	• Solicit blood samples from the public on a volunteer basis, no payment for samples
Genomics Collaborative[65]	Research companies and academic institutions	• International tissue bank collects tissue through physicians who are part of a protocol, and perform consent procedures approved by local IRB • A third-party escrow agent follows patients in longitudinal studies while protecting patient confidentiality from company and their clients
Impath Predictive Oncology[66]	Pharmaceutical and biotechnology companies, and physicians	• Cancer registry database through a network of physicians; samples obtained with informed consent
LifeSpan BioSciences[67]	Pharmaceutical and biotechnology companies	• Samples obtained from medical institutions, possibly governed by local IRB • Each institution collects its samples and obtains informed consents to the extent required by applicable laws, regulations, and ethical standards
Peterborough Hospital Human Research Tissue Bank[68]	Research companies and academic institutions	• Donated with informed consent process and signed document
Serologicals Corporation[69]	Biological products to life science companies	• Solicit blood samples from the public, compensation is given for samples

There is nothing illegal with these approaches, but they have opened new categories of potential conflict of interest and discomfort for many. Patient advocates need to know that these kinds of companies exist, and how Cooperative Groups and their member institutions may or may not interact with them.

Patient Organizations

"In an effort to halt medical researchers and drug companies from serving their own ends instead of any particular disease, patient groups are starting to acquire patent rights to genes and setting up of banks of tissue samples for researchers to use."[70]

The following example illustrates the trend of organizations who sell tissue for specific kinds of diseases and conditions:

For Instance: PXE International[71]

PXE (pseudoxanthona elasticum) International is a 501(c)3 organization founded in 1995. Their mission is to fund research, support individuals and families with PXE, and to provide resources to clinicians. They have established a tissue bank for people afflicted with PXE, a genetic disorder, and have become involved in other patient advocacy groups and at least one biotech company. This is how their tissue bank has worked to date:

- Families with the disease were contacted, and donated tissue and blood samples.
- Samples were offered to researchers with the condition that PXE would have a stake in any intellectual property that was developed.
- PXE gene was discovered in 2000. PXE acquired the patent rights.
- While PXE is a rare disease, the gene is associated with skin wrinkling and heart disease.
- PXE stands to profit from licensing the gene to companies that want to do additional research.
- In seven years, PXE International has grown to include an international 19-lab consortium, more than 52 support offices worldwide, a private blood and tissue bank, and a database registry of thousands of affected individuals

While there is nothing legally or technically wrong with the way PXE International was created, there are critics of this approach. Here are a few examples of the pros and cons:

Pros	Cons
• Patients take control of the research process by providing donated samples and fund raising to scientist • Patients as a group can benefit from money raised • Research is done in a rare disease that would not otherwise be accomplished	• May work only in rare diseases where patients and families can be rallied • Is it a good idea for anyone to "own" a gene? • Potential conflict of interest by owning tissue and close ties to other companies

Who Owns the Tissue?

Even though tissue comes from an individual, they do not necessarily own it or the things that may be produced from it. Institutions, companies, and Cooperative Groups include statements to this effect in their consent forms. It is the intellectual use of the tissue, and not the tissue itself that could produce something of commercial value. The issue of tissue ownership is complex, and can be viewed from several perspectives: the legal view, the philosophical view, and the real world view.

The greater the value of tissue, the greater are the concerns about ethical issues regarding tissue.

One of the concerns that well-informed patients have is how tissue may be used in the future, and if entities are profiting from the use of their tissue.

The Legal View

Legally, it has been determined that a person has no property rights to tissue that is taken out of the body, based on the premise that a person would not take the tissue and create a product out of it. The court ruled that those who do create a viable product (i.e. cell line), can declare ownership and own a patent.[72,73,74] Since this case set a legal precedent, we are listing facts surrounding it:

The Moore Case[75,76]	
Details	• 1976: John Moore diagnosed with a rare cancer (hairy-cell leukemia), which affects the spleen • October 5, 1976: John Moore checked into the UCLA medical center and subsequently had a splenectomy. Dr. Golde was his doctor • Original 1976 consent was for surgery. Moore declined to relinquish rights to potential products developed from his tissue • September 1983: Moore presented with a second consent form asking for use of his cells in research, and to waive his rights to any cell line or product that might be developed • Moore became suspicious that his cells were being used without his consent and consulted an attorney • Dr. Golde and his research assistant filed a patent that was assigned to the Regents of the University of California and named Golde and Quan as the inventors. The patent was on a cell line known as "Mo."
Decision	• The California Supreme Court recognized Moore's right to seek compensation for injuries suffered as a patient • The court did agree with the claim that Moore's tissue or property was taken unlawfully • The Court did not recognize injuries he might have suffered as a source of human tissue used in scientific research and commercial product development • Found a duty on the part of physician/researchers to make fuller disclosure than was made to Moore • Declined to acknowledge a claim for unlawful taking or "conversion" of Moore's "property" • Position statement: Societal interests in new medical products outweigh individual interests. The biotechnology industry would suffer if the courts chose to require scientists to obtain prior approval from patients for any and all uses of their tissue

Unless it is covered in the informed consent, courts have upheld the right of institutions to use specimens as they see fit, even if it is used to develop something for commercial use.

In other words, supplying the "raw materials" doesn't give you the right to "cash in" on the finished product. This may be an issue on which there will be no consensus, even in the patient advocacy community.

The Philosophical View: One Dissenting Opinion to Moore

Main Objections to the Moore Decision[77]	
Injustice Between Patients and Researchers	• If researchers and companies make profits from their contributions, why should tissue contributors be left out? • How is the value of tissue calculated? • How to compensate when knowledge gained is only through aggregation of many samples?
Indignity and Injustice Among Contributors	• Current system criticized for not respecting the dignity and autonomy of contributors. Withholding "information necessary to make a considered judgment"[78] about tissue contributions abrogates the requirement of "respect for persons," one of the key principles of the Belmont Report.[79] • New consent forms have been developed, but have generated their own controversies[80]
Mistrust	• Without disclosure, patients might distrust doctors, researchers and biotechnology companies • Disclosure of tissue use, without addressing the compensation, might also create distrust • If the system is perceived as unjust, people may not make their tissue available for research

In most cases, products developed from biological samples are not uniquely dependent on the particular sample from which they were developed. It is also true that most tissue research has not led to a commercial product.

The Moore decision, while only legally binding in California, is now guiding the question of payments for tissue across the country.[81] As a result, there is much confusion, and many inconsistencies that are applied. Here are some examples: Should all tissue be treated alike? Should it be sold or donated?

The Real World View

The realities of how the process actually works can differ from the theoretical applications of law and ethics.

Patients can have access to reports and slides used in their own diagnosis. It is only when a person wants to "take" the tissue that he/she may face problems. This arises because most patients sign over their legal rights for tissue or specimens that come from their body in order to have a surgical procedure. While technically, patients may have the right to cross out sections of the surgical consent, most do not know this and are pre-occupied with more immediate concerns. There have been isolated cases where patients have successfully obtained their tissue, but these are rare.

Some consent forms offer separate consent sections for tissue, but it is still not consistent across the country. Patient rights vary greatly from state to state.

The issues involving tissue use are being addressed in Cooperative Groups. For example, the consent form for an ACOSOG trial contains a section entitled "What about the use of my tissue for other types of research?" This section contains language that is similar to most Cooperative Groups, and provides critical information that can help an individual make an informed decision, including:

- Listing the purpose "this tissue may be used to learn more about cancer and other diseases"
- Clearly stating that participants can refuse to give consent and that if they give consent, they can withdraw that consent at any time
- Explaining how confidentiality will be protected
- Addressing the issue of compensation with the statement, "Your tissue will be used only for research and will not be sold. If research done on your tissues helps develop new products in the future, you will not be paid."

For more information, see the informed consent form in your Handout section.

Conflict of Interest

Tissue, and its use, has created new kinds of conflicts for all tissue sources. We have touched on this important topic in Chapters 1, 2, and 4 to give you food for thought. The immensity and uncertainty of this subject could take up an entire module by itself.

NIH Policy[82,83]

The NIH Policy Manual lists guidelines to use to avoid conflict of interest for government employees, and is regularly suggested for use by all who receive NIH funding. The latest date we could find for this policy was June 19, 1998, and may not cover all of the current conflict of interest issues that are surfacing throughout the U.S. For more information, please see the Web sites listed in the footnotes.

Cooperative Groups have established their own Conflict of Interest Committees that deal with required government forms for publicly-funded researchers.

Patient advocates may be able to help Groups and investigators think through new potential conflicts of interest in discussions, but only after we truly understand and think through the ethical standards, and apply them to our own actions as well.

Thought Provokers for Chapter 3

These questions are designed to help you think about how to apply the information you have just read. Please use the other side if you need more space, and bring these to share at the upcoming workshop.

1. What kind of harms could a person experience by donating tissue for research?

2. What kind of protections can be put into place to provide as much protection as possible?

3. How can you, as a patient advocate, help ensure that cancer research takes place while still protecting people from harm?

CHAPTER

4

TISSUE ISSUES

As discussed in the previous chapters, there are many issues that surround the use of tissue in research. This chapter will list some of these issues, although it does not contain a comprehensive discussion.

All of these issues, and probably several more, are important to keep in mind as patient advocates participate in Cooperative Group committees, and read protocol and consent forms.

General Tissue Issues

General Tissue Issues Involved in Research	
Collection, Storage, and Shipment	• Tissue and specimens are limited in size (some samples are too small to use for anything but diagnosis); must be carefully handled to ensure usability • Some pathologists will not share specimens with outside researchers, fearing loss of control of the tissue • Some pathologists do not know how to use special techniques for collecting, storing and shipping specimens for genetic analysis • Fixative problems with tissue that may change tissue properties: e.g. Will it be different than in the body, can markers be found, etc.? • Storing and handling specimens is expensive and highly specialized, so centralized banks have been established
Privacy and Confidentiality	• Genetic studies can reveal information about a person that could be used against them by third parties (i.e. insurers, etc.) • Anonymous specimens have limited use in research • Coded specimens can be somewhat protected, but identity can be known to at least some personnel involved in tissue storage and use • Certificate of Confidentiality is the best protection available, but has never been tested in court • Determining when consent for unspecified use should be obtained • Resolving unclear conditions when no further consent is needed (e.g. difficulty of assessing "minimal risk," de-identifying samples) • Determining when, and how, to involve community leaders or family is also unclear
Differences in Tissue	• Risks vary greatly between different kinds of genetic (inherited) and somatic (tumor-related) tissue research • Even though research with somatic tissue focuses on genomic changes in the tissue, germline DNA is still available

Other Issues Involving Tissue and Its Use

In Pathology Departments

Many pathologists consider themselves patient advocates, even though most never talk to patients directly. They consider themselves guardians of specimens, and carry a deep responsibility to protect each specimen.

Some pathologists might send a representative sample of the tissue to the Cooperative Group PCO if their patient specifically requests it, but others will not.

Issues For Pathology	
Funding	• Pathologists are just beginning to be reimbursed for time on a protocol • Reimbursement may be based upon whether the specimen collection is integral to the study[84] • Lack of reimbursement makes it difficult for institutions to invest in the new technologies needed for special collections
Status	• Some treat pathologists as service providers instead of part of the medical team • Other disciplines sometimes treat pathology as a background event rather than an integral part of the research being conducted
Small/Rare Inventory	• Depletion of tissue "inventory" due to small size of some tumors or the rarity of tumor type
Logistical	• Paperwork/administrative burden of specimen collection for research

In Tissue Banks

Tissue banks (including those in Cooperative Groups) deal with most of the issues presented in this Module. Here are some that are unique to them:

Issues for Tissue Banks	
Tissue Collection Techniques[85]	• Sometimes difficult to find sources of matched tissue (cases of cancer and normal tissue). Sources include surgical resections, autopsy tissues, remnant serum/plasma specimens, labs, etc. • Difficulty in finding properly preserved specimens for a specific research purpose • Determining the conditions under which existing collections may be used for research • Coordinating specimens from hundreds of institutions can be a problem. All tissue may not be prepared in the same way
Tissue Processing and Storage[86]	• Varies according to each individual investigator's protocol • Widely differing and exact procedures; sometimes requires unstained or limited Hematoxylin and Eosin stained sections. Tissue has to be flagged for use in surgery • All tissue may not be housed in one place (i.e. Cooperative Groups)
Shipping[87]	• Varies with the type of tissue collected • Specific protocol procedures requiring same day or batch shipments
Equitable Distribution[88]	• Prioritizing studies within the Cooperative Group who funds the bank • Complicated procedures when sharing tissue with non-Group researchers (can be required with federal funding) • Rare or small tumors may be depleted quickly; not available to everyone • Continual focus on how to get tissue to multiple investigators
Quality Control[89]	• Differing parameters based on different kinds of tissue needs • At no time are specimens compromised to obtain tissue for research
Biohazard and Infection Control[90]	• Need to prevent accidental exposure to infectious agents • Must "assume full responsibility for informing and training all personnel in the dangers of and procedures for safe handling of these and other human tissues" • Keeping track of required forms from each investigator

In Cancer Research

Cancer researchers face tougher procedures and also greater opportunities for conflict of interest than ever before:

Issues For Cancer Research	
Balancing Science While Protecting Patients	• A constant need to advance science that must be balanced by all possible ways of protecting people, and their data, from being misused by third parties • HIPAA regulations require new procedures and database systems to handle them • Currently, no far-reaching legislation prohibits the use of personal information by third parties (e.g. insurers, employers, or businesses)
Scientific Value vs. Individual Control	• Science deals with specimens as isolated units, separate from the person. • Removal of body tissue can intrude on a person's individual autonomy, and psychological well-being[91] • Specimens collected for one purpose, can sometimes be used beyond its original intent (i.e. blood samples from babies for PKU testing)[92]
Conflicts of Interest	• Many scientists patent genes that lead to contracts for personal monetary gain with industry, or test new agents for healthy incentives • NIH Cooperative Research and Development Agreements (CRADAs), to fund discoveries that lead to commercialization

For Example:
CALGB 9761 is designed specifically to detect **occult micrometastases** (single tumor cells or minute clusters of tumor cells in metastatic sites) in patients with Stage I non-small cell lung cancer (NSCLC), but includes no treatment. This trial requires fresh and frozen bone marrow, as well as half of several lymph nodes.

This kind of trial is extremely important, based on the scientific knowledge that can be learned, but scientists fear that it may be even more difficult to gain timely accrual since no treatment is involved. Enrolling in a clinical trial like this requires a purely altruistic act.

Cultural and Community Issues

"Western science goes to great lengths to dehumanize the humanness or life-force of human genes; hence, terms such as "specimens," "materials," "properties," and "collections"... ignore the essence of life contained within."
— W.L. Freeman The Role of Community in Research with Stored Tissue Samples

Cultural and Community Issues	
Respect for Beliefs and Traditions in Various Cultures	• For some Native Americans, genes and many other things like genes, the afterbirth or placenta and even sacred sites have a "life force." It is contrary to their traditions to "objectify" human organs or genes[93] • Research practices emphasize consent by an individual which may be in conflict with some cultures where decisions are made by families rather than by the individual[94]
Legal/IRB	• Although many community/ethnicities have cultural and historical beliefs about research, Native American Tribes have legal standing to force researchers to seek approval by the Tribe[95] • Most Tribal Centers, Clinics, and Councils have IRBs which need to approve a genetic research project prior to implementation within a Native community[96]
Lack of Representatives Within Professional Community	• There are fewer minorities represented within medicine and research • People from certain cultures may not be willing to consent to research if no researcher represents their culture. It is more difficult to gain consent for Native Americans to participate in genetic studies since there are no Native American genetic counselors or genetic researchers in the U.S.[97]
Biological Differences	• Certain ethnicities may have unique biomarkers that either lower their risk of some types of cancer (e.g. Native Americans), or raise risk (e.g. African Americans)[98] • The unique biomarker theory is still unknown due to low numbers of samples within certain populations • Some ethnicities may react differently to pain medications or treatments, which may skew study results or have an impact on accrual because of attitudes, beliefs and reactions

Cooperative Group patient advocates need to understand cultural and community issues so they can be considered during Group discussions.

Notes

Thought Provokers for Chapter 4

These questions are designed to help you think about how to apply the information you have just read. Please use the other side if you need more space, and bring these to share at the upcoming workshop.

1. How can you, as a patient advocate, help with the research issues listed in this chapter?

2. Why are there issues between balancing scientific research and individual control?

3. How can you bring cultural and community issues into Cooperative Group discussions?

APPENDIX A

RESOURCES/REFERENCES

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Web Sites	American Society of Law, Medicine and Ethics www.aslme.org Association of Science-Technology Centers http://www.astc.org/funding/sepa.htm Cooperative Research Centre for Discovery of Genes for Common Human Diseases http://www.genecrc.org/index.htm Food and Drug Administration http://www.fda.gov Genomes to Life http://doegenomestolife.org Google Directory http://directory.google.com Select science, biology, genetics

continued

Web Sites (continued)	National Cancer Institute- Center for Bioinformatics http://ncicb.nci.nih.gov/ Index of Web sites http://www.nci.nih.gov/AboutNci/ncisites: News Center http://newscenter.cancer.gov/ Resources Development Branch http://www- cdp.ims.nci.nih.gov/rdb.html *Science* Magazine http://www.sciencemag.org/feature/plus/sfg/ Science Education Partnership Award (SEPA) http://faculty.washington.edu/chudler/sepa1.html SCOPE Science Controversies On-line Partnerships in Education http://scope.educ.washington.edu/ The Human Genome Project http://www.genome.gov/Pages/EducationKit/ US Department of Health and Human Services HIPPA Medical Privacy see http://www.hhs.gov/ocr/hipaa/ Office of Human Research Protection http://ohrp.osophs.dhhs.gov/ **Professional Organizations** American Society for Clinical Pathology www.ascp.org American Society of Cytopathology www.cytopathology.org American Society of Hematology (ASH) www.hematology.org Association for Molecular Pathology www. ampweb.org College of American Pathologists www.cap.org International Society for Biological and Environmental Repositories www.isber.org **Government Regulations & Guidelines** Office for Protection from Research Risks , Issues to Consider in the Research Use of Stored Data or Tissue available at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm
Endnotes	See end of document

APPENDIX

B

TRAINING PROGRAM

The Coalition of National Cancer Cooperative Groups, Inc. is sponsoring this training program for patient advocates in Cooperative Groups. The following plan explains how the training program is being developed, implemented, and evaluated.

Goals

Provide education, training and ongoing professional support that will enable advocates to:

- More effectively inform and influence the cancer clinical research process
- Stay current with the ever-changing issues and aspects of clinical research
- Ultimately help increase patient accrual to clinical trials

The Coalition's Patient Advisory Board (PAB) confirmed evidence of need for advocate training in a survey in July 2000. Of 31 advocates who responded, 58 percent had no prior training or exposure to the clinical trials system. Nearly 100 percent said they would benefit from training. Mentoring, study guides, and workshops were ranked as the most valuable training aids.

Target Audience

Cooperative Group patient advocates include survivors, family members, and caregivers. They represent all major cancers, and age groups from 30 to over 70. This program will serve nearly 120 advocates per year in all Cooperative Groups. Many of these advocates represent patient advocate organizations or are involved in efforts in their communities. Once developed, the Coalition intends to offer this program to patient advocate organizations and other institutions.

Training Program

This training program relates directly to the function of a Cooperative Group patient advocate, instead of a general education program to increase knowledge with no focus on application. Patient advocates will immediately apply their knowledge in the committees in which they participate, and will be able to give quick feedback on what works and what should be added or adjusted.

Existing materials from various sources are continually identified and incorporated, and some original material will be created. The interactive training program includes:

- Multi-faceted Training Modules:
  - Self-Study Guides that coincide with each training workshop
  - Training Workshops to be given at Cooperative Group meetings
  - Action Plan for each individual and Cooperative Group advocate team
  - Evaluation Program (advocate and Cooperative Group feedback)
  - Web-based curriculum for interactive learning experiences

Advocate Training Modules

"Clinical Trials 101"

The first five modules contain basic information.

1. ***Cooperative Groups***
2. ***Cancer Clinical Trials***
3. ***Drug Development***
4. ***Surgical and Radiation Therapies***
5. ***Protecting Research Participants***

Additional Modules

6. ***Tissue and Its Use***

APPENDIX C

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1818 Market Street, Suite 1100
Philadelphia, PA 19103
Tel: 215-789-3600
Fax: 215-789-3655
www.cancertrialshelp.org

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