

Research Advocacy Network

Advancing Patient-Focused Research

Understanding Pathology and Tissue Research

AN ADVOCATE'S GUIDE



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INTRODUCTION

Why Was This Guide Developed?

This guide was developed to help advocates and other interested individuals understand pathology as it relates to cancer. The guide also explains tissue research and its importance in identifying causes, treatments, and potential cures for disease.

As you will see when reading this guide, progress in cancer research depends on the availability of tissue biospecimens – both healthy and cancerous. Advocates can play a key role in helping patients and their families understand the need for tissue and help safeguard its appropriate use.

It is hoped that this guide will provide a foundation of pathology knowledge for advocates to draw on as they participate in existing groups or develop new activities to influence research.

How Is This Guide Organized?

This guide is organized into 8 chapters, each of which covers a specific topic. Chapter 1 provides an introduction to pathology – What is it? Who does it? What are its uses? Chapter 2 describes the pathology report or the document generated by pathologists. Chapter 3 considers issues in clinical pathology, which essentially refer to tests that are performed on the tissue. Pathology in cancer research is explored in the next two chapters, with Chapter 4 focusing on what we can learn from tissue pathology and Chapter 5 focusing on the issues it raises. Chapter 6 considers the many ethical aspects of tissue donation and research. Chapter 7 lists some questions that advocates may pose and Chapter 8 explores some of the issues that are important to advocates. Chapter 8 also contains a glossary which gives definitions for many terms that may be unfamiliar. The Appendix describes some of the ways that advocates are involved in multiple areas related to pathology and tissue research.

The Sources section at the end of each chapter lists websites, booklets, books, and/or research articles from which information in that chapter was obtained. Additional sources that you may find useful are listed in the text of each chapter.

Acknowledgements

As advocates try to work within the system to advance research it is important to understand the basic tenets of the science. By a better understanding advocates can identify and illustrate the issues and problem-solve to support solutions. The issues in research involving biospecimens and tissue were the motivation for developing this manual. We hope that this information will be helpful to advocates and others interested in advancing the science and improving care for cancer patients. This publication was developed with funds from the Advocate Core of the Breast Cancer Centers of Excellence for Individualization of Therapy at Indiana University (Dept. of Defense grant). We gratefully acknowledge the following contributors/reviewers:

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CHAPTER 1. INTRODUCTION TO PATHOLOGY

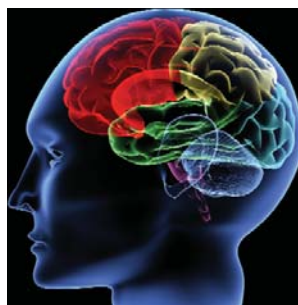
What Is Pathology?

Pathology is the branch of medicine that deals with structural and functional changes in tissue that cause, or are caused by, disease. This guide focuses on the tissue changes that are associated with cancer.

What Is Tissue?

A tissue is a group of cells in the body that performs a similar function. Tissues form organs, which are structural and functional units that have specialized functions.

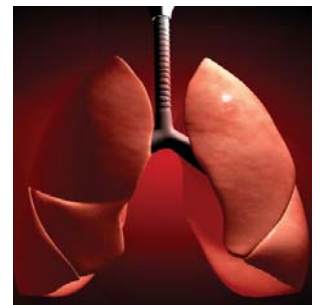
Examples of organs:



BRAIN

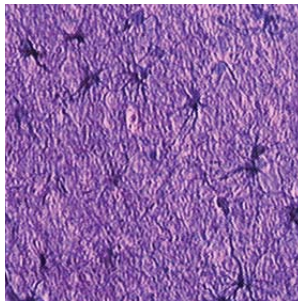


MUSCLE*

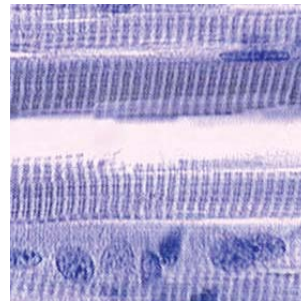


LUNG

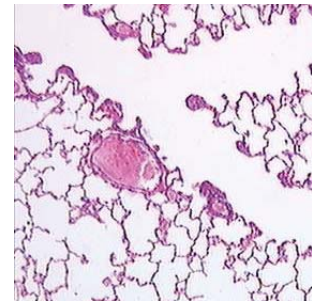
Examples of tissues:



BRAIN TISSUE



SKELETAL MUSCLE TISSUE



LUNG TISSUE

The histology images were provided to the HealCentral Digital Library (www.healcentral.org) by Roger A. Gorski, PhD. Copyright: The Regents of the University of California Copyright and usage information: <http://creativecommons.org/licenses/by-nc-sa/3.0/>

*Each skeletal muscle is considered an organ. "A whole skeletal muscle is considered an organ of the muscular system." Source: Anatomy training manual of the government "seer.cancer" module

Other Terms for Tissue

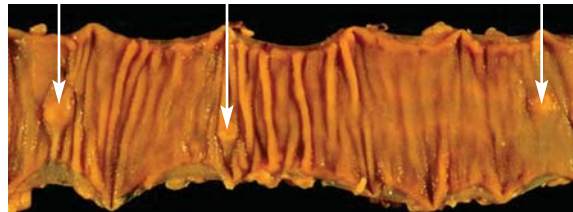
The term tissue is also used to describe a portion of a tissue sample selected for examination. In this context it is often called a specimen or biospecimen. Biospecimens can be small samples of any bodily tissue, fluid, or other substance. The terms tissue, specimen, and biospecimen are often used interchangeably, but sometimes the former are used together as in "tissue specimen." The following table lists some of the types of biospecimens used in cancer research.

Examples of Biospecimens Used in Cancer Research

- Blood
- Bone fragments
- Bone marrow
- Central nervous system fluid (cerebrospinal fluid or CSF – liquid around brain and spinal cord)
- 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

Table adapted from Coalition of Cancer Cooperative Groups, Inc. *Cancer Research: A Guide to Clinical Trials. Tissue and Its Use*. Available at: www.cancertrialshelp.org/patient_content/pdMainContent.aspx?intAppMode=5. Accessed March 20, 2008.

Cancerous tumors of the lower intestinal tract. This picture shows three tumors in the bowel, the relatively circular growths near each end and near the lower middle.



Who Are Pathologists?

Pathologists are medical doctors who specialize in pathology. They examine tissue and cells under a microscope or use tests to determine features of a disease. They perform analyses and provide reports to clinical teams or oncologists to make treatment decisions. Pathologists may also be involved in medical research. Several different types of pathologists are listed in the following table. Many pathologists specialize in cancer and even specific cancer types. For example, hematopathologists may specialize in cancers of the blood such as the leukemias and urologic pathologists may specialize in prostate cancer.

Some Specialties Within Pathology

Anatomic pathology: diagnosis and descriptions based on analysis of the tissue (i.e., visible changes in the tissue)

Clinical pathology: diagnosis and descriptions based on laboratory tests (i.e., biochemical changes in the tissue)

Dermatopathology: pathology of the skin

Hematopathology: pathology of the bone marrow and blood clotting

Forensic pathology: pathology within a legal context (often takes the form of pathology determined from tissue after death)

Historically, pathologists have been behind the scenes in medicine. They often work in laboratories located inside hospitals. Here the pathologists analyze tissue removed from patients during surgery, blood samples, saliva samples, or samples obtained via needles. Often the pathologist will place a tiny portion of the biospecimen on a microscope slide and stain it with specialized dye to mark the cells or other structures. This is referred to as histology. The following shows a histology sample of blood that has been magnified many times.

Histology sample of blood stained to show the different types of blood cells (round structures).

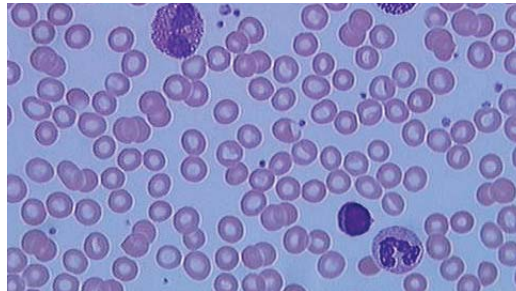


Image courtesy of Health Education Assets Library. Available at: <http://www.healcentral.org/copyrights.jsp>

Pathologists also examine tissue while the patient is undergoing surgery. In some cases, a sample of the tissue is immediately frozen (commonly called a frozen section), then a slide containing the tissue is closely examined under a microscope. From this examination, the pathologist may make a diagnosis that guides the course of surgery and/or other therapy. For instance, what may have initially been thought to be an infection-related process may turn out to be a tumor that the surgeon can then remove. The pathologist may also help determine the margins of resection for a tumor (i.e., help the surgeon determine where to cut). For a thorough discussion of the diagnostic process and issues related to tissue, see the Guide cited at the end of this chapter called *Tissue and Its Use* published by the Coalition of Cancer Cooperative Groups, Inc.

Pathologists work in several different settings, including universities, independent laboratories, and laboratories sponsored by industry or the government. Although pathologists still work in hospital laboratories and operating rooms, their roles in medicine and research are becoming much more visible. In these settings, pathologists may run medical tests or may conduct research aimed at finding links between pathological tissue and disease. For instance, pathologists may attempt to find biomarkers in tumor tissue. Biomarkers are laboratory measurements that reflect the activity of a disease process. They often take the form of proteins that are used to identify cancerous cells.

As noted previously, pathologists may examine tissue with the naked eye or under a microscope to analyze its structure and appearance. However, pathologists may also conduct tests on the tissue to determine whether it contains a substance or gene of interest, or to measure the level of a substance. Pathology tests often detect proteins, but may also examine our genetic material (DNA and RNA), as well as the by-products of chemical reactions, or drug levels.

How Are Tissue Samples Collected for Pathological Analysis?

Tissue samples may be collected by a number of different methods depending on the location of the cancer and the type of test. Blood samples are often drawn from veins in the arm, and saliva is obtained from the mouth. Tissue samples from solid tumors may be obtained surgically, or by using a fine needle or needle with a hollow core (i.e., core needle biopsy) to pull out cells. Another method involves the use of a flexible, lighted instrument called an endoscope that is inserted into one of the body's natural openings. The endoscope allows the physician to see abnormal areas on the lining of organs and pinch off tiny bits of tissue. Samples may be taken from the skin following a local anesthetic. Cells for genetic testing may be collected from several sources such as scraped from the inside of the mouth or cervix, isolated from a tumor specimen that has been surgically removed, or from white blood cells isolated from a blood sample. For more complete information on how tissue samples are collected and processed, please see the sources cited at the end of this chapter.

Some Methods of Tissue Collection	
Blood sample from vein	Surgical excision
Saliva	Endoscopy
Needle biopsy	Cells scraped from cheek or cervix

What Types of Tests or Analyses Do Pathologists Perform?

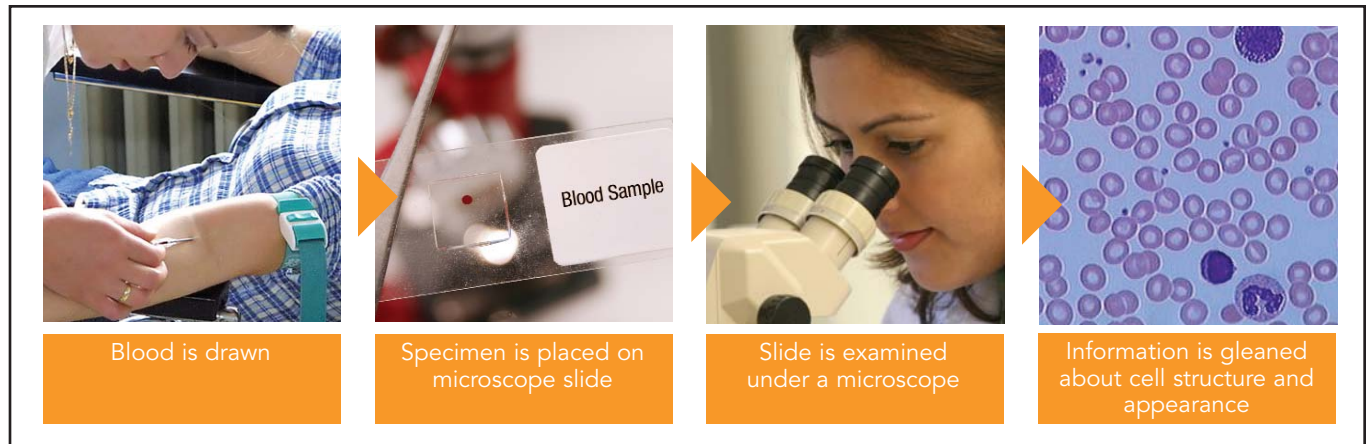
The following list provides some examples of the types of tests or analyses pathologists perform.

1. Analyses of the general structure and appearance of tumors

In this type of overall analysis (sometimes called gross analysis), the pathologist simply looks at the tissue with the naked eye and notes its features such as color, appearance, and size.

2. Analyses of the structure and appearance of cells

In this type of analysis, the pathologist examines a tiny portion of the tissue under a microscope to see the structure and appearance of cells. A PAP smear is an example of this type of analysis. The pathologist may also examine blood or a small section of a solid tumor by placing a drop of blood or a thin slice of the tumor tissue on a microscope slide and covering it with a piece of glass called a coverslip. The slide is examined under the microscope before or after staining.



3. Tests to examine the levels of cancer biomarkers in the blood or other fluids

In these tests, pathologists analyze biospecimens to determine the presence and levels of selected cancer biomarkers in the blood or other fluids such as urine. Biomarkers are usually proteins that are produced by cells that may potentially indicate cancer. An example is prostate specific antigen (PSA), which is a protein produced by the prostate. High blood levels of PSA have been associated with prostate cancer and other disorders of the prostate.

4. Tests to assess an individual's genes or chromosomes

In these tests, the pathologist examines a person's genes or chromosomes either directly or indirectly. These tests may be used to determine diagnosis, recurrence, cancer subtype, or prognosis. An example of this type of test is Oncotype DX[®]. This test examines 21 genes using an RNA test—RNA is a chemical that helps transfer information from our DNA into proteins. The test results consist of a recurrence score that helps determine how likely breast cancer is to return. This test is conducted using real-time, reverse-transcription polymerase chain reaction, a method that is described in Chapter 4.

Tests for alterations in several genes called BRCA1 and BRCA2 (for breast cancer) represent yet another example of genetic testing. Alterations in the BRCA1 and BRCA2 genes have been associated with an increased risk of breast and ovarian cancers. Tests for alterations in BRCA1 and BRCA2 are usually done by taking a blood sample. The DNA in the blood is then amplified using the polymerase chain reaction described in Chapter 4. The sequence or spelling of the gene is then analyzed using one of several different methods. The National Cancer Institute's website provides more information on BRCA genes: <http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA>.

Immunohistochemistry: A Method Used to Detect Proteins

Biomarkers are often proteins. One of the most common methods used to detect proteins is called immunohistochemistry. This technique takes advantage of the method our immune system uses to rid the body of foreign proteins – namely, antibodies.

In immunohistochemistry, a sample in which we are trying to find a specific protein is placed together with antibodies that bind to that protein. The antibodies are labeled beforehand with some sort of marker, often a fluorescent one that can be seen under a fluorescent microscope. The antibodies are mixed with the sample in a test tube and given time to bind or pair. If the protein is present in the sample, the antibodies will bind and a visible colored label will be seen under the microscope.

What Is Done With the Information Obtained by the Pathologist?

In medicine, pathologists prepare reports describing their findings, as described in detail in the next chapter. These reports help determine the course of therapy for patients. However, information obtained by pathologists may also be used for research, if the patient consents. This research may be designed to determine whether people are at increased risk for cancer or its recurrence, to predict response to a therapy, to classify the cancer into subtypes, or to determine the cause of cancer. In many cases, the goal of the research is to develop a test that would have clinical value, such as in diagnosis, prevention, or treatment.

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CHAPTER 2. THE PATHOLOGY REPORT – USES IN CANCER DIAGNOSIS AND TREATMENT

What Is a Pathology Report?

A pathology report is a document that a pathologist generates from the analysis of a tissue specimen. The report contains information about the following:

- An individual's diagnosis
- A description of the tissue that can be gleaned from simply looking at it without a microscope, such as color, size, orientation, and appearance
- The appearance of the biospecimen as seen under a microscope called microscopic analysis
- A prognostic report section that lists the results of specific tests that were performed on the biospecimen (often, but not always, included)
- A comment section in which pathologists may add information about tests that still need to be completed or provides more information about the diagnosis. Other pathologists include this information in the preceding sections.

Several resources are available that describe and provide examples of the information contained in a pathology report, including the Y-ME booklet *Understanding Your Pathology Report*, the Doctor's Doctor website, and the online article by Dr. EO Uthman, both listed at the end of this chapter.

Uses of the Pathology Report

The pathology report is used to establish a patient's diagnosis. If the biospecimen is determined to be cancerous, the pathology report can be used to predict the behavior of the cancer. Important information in the pathology report includes the cancer's stage, histological grade and type (e.g., location and type of cells involved). Information about tumor biomarkers obtained from other tests may also be included here. Taken together, this information is used to help determine the appropriate treatment and how likely it is that treatment will be successful. The report can also help determine prognosis – the likely outcome or course of the cancer – including the chance of recovery or recurrence. It is important to note that the prognosis in the pathology report is based on the natural course of the disease, independent of any treatment.

Pathologic staging

An important piece of information in the pathology report is the overall stage of the cancer. Staging is a method for determining how much cancer there is in the body and where it is located. It indicates the extent or severity of cancer based on an analysis of the original or primary tumor. Although pathologic staging is still very important, it is possible that classifications of cancers will change and become more specific as more biomarkers are discovered.

Cancers are staged by a number of different methods. Often the staging method depends on the type of cancer. Here we describe several common methods of cancer staging that are applicable to a variety of different cancer types.

A commonly-used overall staging method described by the National Cancer Institute uses a scale of 0 (zero) to IV (four) to rate the cancer stage, with higher numbers indicating more advanced cancer. Although the precise definitions of each stage are different for each kind of cancer, stage I usually indicates small localized cancers and stage IV usually indicates cancers that have spread to distant regions beyond the tumor's original location. The following table lists general information about each stage.

Stage	Definition
Stage 0	Carcinoma in situ (early cancer that is present only in the layer of cells in which it began).
Stage I, Stage II, and Stage III	Higher numbers indicate more extensive disease: greater tumor size, and/or spread of the cancer to nearby lymph nodes and/or organs adjacent to the primary tumor.
Stage IV	The cancer has spread to another organ.

From the National Cancer Institute Fact Sheet. *Staging: Questions and Answers*, 2004

Cancers may also be staged according to the so-called “TNM” classification system. In this system, T refers to the extent (e.g., size) of the tumor, N refers to the involvement of lymph nodes, and M refers to metastasis or the spread of the tumor to different parts of the body. The letters are followed by numbers that indicate the size of the tumor, the extent of tumor spread to lymph nodes, and whether or not the tumor has metastasized. The TNM definitions are shown in the following table. The TNM is brought together as a stage; for instance, T1 N0 M0 = stage 1.

Primary Tumor (T)

- TX: Primary tumor cannot be evaluated
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ (early cancer that has not spread to neighboring tissue)
- T1, T2, T3, T4: Size and/or extent of the primary tumor

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be evaluated
- N0: No regional lymph node involvement (no cancer found in the lymph nodes)
- N1, N2, N3: Involvement of regional lymph nodes (number and/or extent of spread)

Distant Metastasis (M)

- MX: Distant metastasis cannot be evaluated
- M0: No distant metastasis (cancer has not spread to other parts of the body)
- M1: Distant metastasis (cancer has spread to distant parts of the body)

From the National Cancer Institute Fact Sheet. *Staging: Questions and Answers*, 2004

For instance, a tumor that is rated T3 N0 M0 is a large tumor that has not spread to lymph nodes and has not spread to distant parts of the body. Lower-stage cancers that have not spread to lymph nodes or distant parts of the body are more readily treatable and more likely to be in remission than are higher-stage cancers. Thus, stage helps determine how aggressive the treatment should be and how likely it is that treatment will be successful.

Some examples of the different tumor stages can be found at the following websites:

- **Colon cancer:** <http://www.dartmouth.edu/~brenner/gene144-06/rogers.html>
- **Prostate cancer:** http://www.urologychannel.com/prostatecancer/prostate_stage2.html
- **Prostate cancer:** <http://www.biomedcentral.com/1471-2407/7/2/figure/F5>
- **Esophageal cancer:** <http://www.med.nyu.edu/nyuci/cancer/gi/esophageal.html>

Histological grading

Cancers may also be graded on a scale of 1 to 3 or 1 to 4 based on the appearance of cells as seen using histology. That is, pathologists look at the cells on a microscope slide to determine how closely they resemble normal cells from the same tissue. Cells that look normal for that type of tissue are said to be well differentiated or low grade. Cancer cells that look highly abnormal are said to be undifferentiated or high grade. The following table lists a widely-used type of grading system; however, it should be noted that not all tumors are graded this way. The higher-grade tumors (3 and 4) tend to grow more rapidly and spread faster than the lower-grade tumors. Thus, tumor grade can be used to help determine treatment and prognosis.

Histological Grades
GX: Grade cannot be assessed (Undetermined grade)
G1: Well-differentiated (Low grade)
G2: Moderately differentiated (Intermediate grade)
G3: Poorly differentiated (High grade)
G4: Undifferentiated (High grade) Note that some cancers are graded from 1 to 3

From the National Cancer Institute Fact Sheet. *Tumor Grade: Questions and Answers*, 2004

Tumor typing

Tumor typing refers to the specific classification of tumors based on the organ in which it was found such as breast, prostate, stomach, or liver. Organs are made up of different types of cells and the tumor is often classified based on the type of cells involved, as shown in the following table. This is referred to as histological typing because it is based on histological analysis. Tumor typing is becoming increasingly specific as tests are developed that detect the presence or level of a given protein and the genetic profile of the tumor. An example of this increased specificity is in large B-cell lymphoma, the most common subtype of non-Hodgkin's lymphoma. Although 40% of patients respond to current therapy, the remainder do not. Using DNA microarrays (described in Chapter 4), a group of investigators found that tumors of different individuals with this disease showed differences in gene expression. Basically, the tumors fell into two groups, one of which was associated with significantly better overall survival than the other. The investigators concluded that the gene expression profiles of the tumors could be used to classify the tumors into clinically significant subtypes. This information can then be used to guide treatment and perhaps assist in the search for treatments directed at the subtype that is less responsive to current therapies.

Examples of Cancer Types Based on Histological Typing

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), accounts for approximately 90% of cancers
Adenocarcinoma	Tumor of the gland, most common type of carcinoma
Sarcoma	Malignancy that arises from connective tissues including soft tissues and from solid tissues (e.g., fat, muscle, bone)
Melanoma	Tumor that arises from the pigment producing cells of the skin or other organs (e.g., the eye)
Glioma	Tumor that arises from a specific type of cell in the brain or spinal cord (i.e., glial cells or the cells that support nerve cells)

Adapted from Coalition of Cancer Cooperative Groups, Inc. *Cancer Research: A Guide to Clinical Trials. Tissue and Its Use*. http://www.cancertrials.org/patient_content/pdMainContent.aspx?intAppMode=5

Tumor biomarkers

As noted previously, tumor or tissue biomarkers are usually proteins that are produced by cells, indicating the presence of disease. In many types of cancers, biomarkers in the blood serum (the liquid portion of the blood) contribute to diagnosis, staging, risk assessment, evaluation of response to therapy, and early detection of relapse. The following table lists some commonly used serum biomarkers for various cancer types.

Examples of Some Common Serum Tumor Biomarkers and Their Clinical Uses

Cancer Type	Serum Tumor Biomarkers	Use(s)
Testicular	Alpha-fetoprotein (AFP) Human chorionic gonadotropin (hCG) Lactic dehydrogenase (LDH)	Diagnosis, prognosis, staging, risk stratification, monitoring disease
Prostate	Prostate specific antigen (PSA)	Screening/early detection, staging
Colorectal	Carcinoembryonic antigen (CEA)	Surveillance*, response to therapy
Liver	Alpha-fetoprotein (AFP)	Prognosis, surveillance, response to therapy
Ovarian	CA125	Tumor monitoring
Melanoma	TA90-IC	Surveillance

*Surveillance refers to the ongoing collection of information about a disease, such as cancer, in a certain group of people. This may include information about whether cancer affects people of a certain gender, age, or ethnic group.

Tumor biomarkers are also found in tissue samples. These biomarkers may be proteins, genes, or other molecules or structures. Tissue biomarkers can be used for tumor typing, such as determining whether certain genes are present in colorectal tumors. The presence or absence of selected genes may then guide treatment, as some genes are associated with more aggressive tumors than others. Tumor biomarkers may also provide potential targets for novel treatments. For instance, breast cancer cells of some individuals show high levels of the protein HER-2. A drug called trastuzumab (Herceptin®) targets the HER-2 protein, which effectively treats the cancer and often improves survival. Thus, individuals with breast cancer are tested for HER-2 levels to determine if they are candidates for trastuzumab therapy.

Spotlight on Biomarkers

In 2005, the National Breast Cancer Coalition sponsored a conference designed to develop a patient-centered, strategic approach to breast cancer biomarker research. This conference culminated in the development of recommendations for biomarker research, including priorities and timelines, to ensure that basic biomarker research translates into clinical applications as soon as possible. These recommendations were recently published in the journal *Nature Reviews Cancer*. Major topics discussed in this article were as follows:

- Unmet potential of biomarker research
- Need for the development and adoption of standards and guidelines so that only biomarkers with clinical value are translated into routine clinical practice
- Improved access to biological specimens, associated clinical data, and information on research studies
- Need for revision of current regulatory framework for cancer biomarker development and use so that it better serves the interests of patients
- Need for collaboration among multiple stakeholders to ensure that biomarker studies are designed to answer important questions, and that suboptimal biomarker assays are not advanced through the research and development pathway
- Need for education of all involved in biomarker development, especially consumer education regarding the principles and standards to which they should hold the research, clinical, and regulatory communities accountable
- Need to ensure that discrimination does not take place on the basis of a disability or medical condition

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CHAPTER 3. ISSUES IN CLINICAL PATHOLOGY



Clinical pathology involves the use of tests, as opposed to anatomical assessments of the tissue, to aid in diagnosis and treatment. Issues in clinical pathology revolve around the validity, reliability, and clinical utility of the tests, as well as test regulation and standardization. More information about these issues can be found in *Genomics in Cancer: An Advocate's Guide and Training Manual*, available for order on the Research Advocacy Network website listed in the sources at the end of this chapter.

Test Validity

Test validity is basically the accuracy of a test. Two important types of validity are analytical validity and clinical validity. Analytical validity refers to how well a test measures what it is supposed to measure. If a person is having a blood test to determine his or her cholesterol levels, the test should actually measure cholesterol and not glucose or another substance. Although this seems obvious, in practice it is sometimes difficult to design a test that measures only the chemical of interest and does not mix it up with another similar substance. Additionally, it is important to design a test that is sensitive enough to measure relevant levels of the substance it purports to measure.

Two of the important aspects of analytical validity are known as sensitivity and specificity. Sensitivity refers to the ability of a test to detect something that is actually present. For instance, a sensitive pregnancy test is one that has a high likelihood of detecting pregnancy when a woman is actually pregnant. Specificity refers to the ability of a test to give a negative result when the thing being detected is not present. For instance, a test that is specific for the flu virus should not give a positive result for the herpes virus – it should give a negative result if a person has the herpes virus but not the flu virus. These concepts are often expressed as false positive and false negative rates.

- **False positive:** A test result that indicates that a person has a specific disease or condition when the person actually does not have the disease or condition.
- **False negative:** A test result that indicates that a person does not have a specific disease or condition when the person actually does have the disease or condition.

Clinical validity refers to the ability of a test to provide clinically relevant information. For instance, we may provide a blood sample to see if we have West Nile virus. The test may work by detecting antibodies in our blood. If we have antibodies, the test will be positive; if not, the test will be negative. Before using this test clinically, it is important to establish that the presence of antibodies in the blood is a good predictor of whether or not we have the disease. If a positive result on the test is a good indicator of West Nile virus infection, then the test is said to be clinically valid.

How Are Tests Validated?

Tests are validated by conducting clinical studies that document the relationship of the test's outcome with an important medical or clinical outcome. For instance, if the test purports to detect response to therapy, then test results would need to show a relationship with reduced tumor growth, patient survival, or another important variable in a clinical study. Such studies provide

scientific proof of the test's accuracy. Without validation in a clinical study, the test's accuracy must be considered unproven.

Test Reliability

Reliability refers to the ability of a test to give the same result each time, even when performed by different individuals in different laboratories. If a test indicates that a tumor is unlikely to recur, the test should give the same result if it is performed again and again, whether by the same person in the same laboratory or by a different person in a laboratory across the country. Unreliable tests are not useful in making diagnoses or treatment decisions.

Clinical Utility

Clinical utility refers to the overall usefulness of a test in clinical practice that is determined by weighing its benefits and drawbacks. Pathology tests should provide some clinical benefit such as information that aids in diagnosis or clinical decision making. A test that could reliably detect 20 common genes associated with a tumor may not be clinically useful if those genes don't predict anything of value for the patient or physician. A test that is extremely difficult to perform, or requires rare technical equipment, may not have clinical utility in routine hospital use, even if it provides clinically useful information.

Test Standardization

Standardization refers to a test's ability to conform to a standard or its evaluation against a standard. Standardization is important so that an individual undergoing pathology testing can be confident that his or her results are accurate. Additionally, standardization is necessary so that results from different laboratories can be compared. The methods and chemicals used by each laboratory should be the same for a given test. For instance, when testing athletes for steroid use, it is important that a sample from a baseball player for the Boston Red Sox is subjected to the same procedures as a sample from a player for the Atlanta Braves. The levels required to give a positive result should be the same.

When conducting research studies involving different treatment centers, it is essential that the tests be standardized so that results can be combined for all patients regardless of where they were treated. Even studies in which all testing is done at a single laboratory should be standardized so that results can be compared against those of future studies.

Sometimes tests that are sold as kits include what is known as an internal standard, which is a sample that contains a given amount of the substance being detected. This standard can then be used to calibrate the test. For example, a test kit might contain an internal standard that consists of 100 micrograms of a protein. When that standard sample is run in the laboratory test at Swedish Hospital in Seattle, the test should find that the sample contains 100 micrograms. When that standard sample is run in the laboratory at St. Louis University School of Medicine, the test should find that the sample contains 100 micrograms. In this way, laboratories can make sure that their test is giving the results it is supposed to and that they are comparable with other laboratories.

Standardization in laboratory tests may be achieved by requiring laboratories to undergo proficiency testing. For example, blood samples may be sent to participating laboratories for the determination of the substance of interest. The results from all participating laboratories are sent to a central facility where they are evaluated and the laboratory is either certified or not, based on its ability to obtain accurate results.

An example of the lack of standardization in cancer is HER-2 in breast cancer. In late 2006, the National Comprehensive Cancer Network published recommendations to address the lack of standardization. The American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) also issued joint recommendations about the lack of consistency in these tests, based on the finding that approximately 20% of the tests are discrepant. ASCO-CAP recommends that laboratories attempt to reduce the variability in the tests by adhering to strict biospecimen handling procedures, among other things. These guidelines also recommend that in order to conduct HER-2 tests, laboratories should show 95% agreement with another validated test. Also, stringent laboratory accreditation standards are recommended, along with proficiency testing and competency assessments. This lack of standardization is critical because in some cases, it may mean that certain drugs are being given to people who will not benefit from them or, conversely, people who could benefit from certain drugs are not receiving them. Research Advocacy Network and the National Comprehensive Network have published Patient Guidelines on HER-2 Testing. These guidelines are available on their websites.



Test Regulation

Pathology tests are regulated differently depending on whether they are sold as kits or services. Tests are considered kits or diagnostic devices if they are marketed as products. Kits contain all of the necessary materials for physicians to conduct the test in their offices or affiliated laboratories. If a biospecimen must be sent to a company's laboratory to be analyzed by them, it is considered a service.

What Are Test Kits?

If a test is sold as a kit it means the test is sold along with all of the materials necessary for physicians to conduct the test in their offices or affiliated laboratories. There is no need to make or synthesize anything additional. Pregnancy tests sold at the drugstore are examples of kits; however, in the case of pregnancy tests, one is not assessing any pathology or disease and thus the kits can be sold directly to consumers.

Kits or diagnostic devices may require approval by the United States Food and Drug Administration (FDA). The amount of oversight the FDA exerts depends on the kit's intended use and its risks. The classification scheme ranges from Level I to Level III:

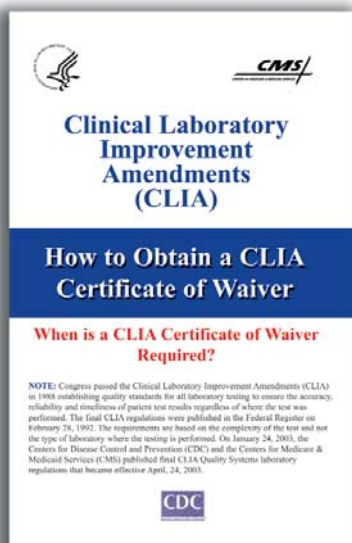
- Level I requires minimal oversight and poses minimal risks to consumers
- Level II requires an intermediate level of oversight and poses an intermediate risk to consumers
- Level III requires the most data and oversight and shows the most potential for harm.

Cancer diagnostic tests are classified as Level III because they provide information that can have a high impact and may alter the course of life. These tests are required to undergo validation procedures to make sure that they are accurate and clinically useful.

Tests sold as services are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. According to these regulations, all laboratories performing these services must be certified to conduct testing on human biospecimens. The essential ingredients needed to conduct the tests are regulated by the FDA. These ingredients may only be sold to organizations that are diagnostic device manufacturers, qualified clinical laboratories, or organizations that use the ingredients to make tests for non-medical purposes (such as academic laboratories).

However, as a growing number of highly complex tests become available, the FDA is increasing its oversight of this area. Some of these tests are beyond the normal expertise and ability of general laboratories and are therefore being regulated to a greater degree. The CLIA regulations are evolving and stricter oversight by the FDA seems to be a trend that is likely to continue as tests become more specialized and complex.

More information on CLIA regulations may be found at the following website: <http://www.cdc.gov/clia/regs/toc.aspx>. These regulations include general as well as specific information on each type of test, including information about test accuracy, validity, and the range or span of test result values that are reportable.



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CHAPTER 4.
PATHOLOGY IN
CANCER
RESEARCH – WHAT
CAN WE LEARN
FROM TISSUE
PATHOLOGY?

Type of Information

Biomarkers

A great deal of research is directed at identifying biomarkers associated with cancer. As noted previously, biomarkers may be molecules in the blood serum (serum biomarkers) or associated with a specific tissue (tissue biomarkers)—often a tumor. Some tissue biomarkers are listed in the following table. Tissue biomarkers can be proteins, genes, chromosomes, or other material. For instance, some researchers employ sophisticated technology to identify differences in the pattern of genetic material in cancerous and normal cells. This strategy may ultimately be used in the clinic to determine whether cells are responding to treatment.

The National Academy of Clinical Biochemistry has issued practice guidelines on biomarkers for multiple cancer types. These guidelines provide an analysis of the various biomarkers used in the different types of cancers, including the level of scientific evidence in support of each. The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network® (NCCN) have also published clinical practice and patient guidelines that include information on tumor biomarkers for several cancer types. The specific guidelines from these organizations can be viewed at the websites listed in the Sources section at the end of this chapter.

Examples of Some Tumor Biomarkers and Their Clinical Uses		
Cancer Type	Tumor Biomarkers	Use(s)
Melanoma	Melanoma Inhibiting Activity (MIA) S100	Staging/prognosis, recurrence Staging/prognosis
Colorectal	Carcinoembryonic Antigen (CEA)	Staging/prognosis, recurrence, monitoring
Liver	Alpha-fetoprotein (AFP)	Diagnosis, staging/prognosis, recurrence, monitoring
Pancreatic	CA19-9	Staging/prognosis; may be used for other purposes under certain conditions
Breast	Estrogen receptor (ER) and progesterone receptor (PR)	For predicting response to hormone therapy in both early and advanced breast cancer

The National Academy of Clinical Biochemistry. Laboratory Medicine Practice Guidelines. Tumor Markers. Available at: <http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/DraftGuidelines/TumorMarkers/TumorMarkersPDF.htm>.

Disease subtyping and classification

Some biomarkers may be used to further classify the cancer beyond its location (e.g., bone marrow, brain, liver, etc.) and cell type (e.g., adenocarcinoma). Subtyping cancers based on biomarkers may be useful in determining prognosis and selecting treatment. For instance, hereditary nonpolyposis colorectal cancer is an inherited type of colorectal cancer that is particularly aggressive. As a result, individuals with genetic mutations that predispose them to this type of cancer are advised to undergo more frequent screenings than those who lack the mutations. Additionally, treatment is more aggressive.

Novel treatment targets

In some cases, the actual biomarker for a given disease subtype is believed to be related to the immediate cause of the cancer and may be targeted with therapy. This is the case for breast cancers that overexpress the protein HER-2. This subtype of breast cancer is often treated with the drug trastuzumab (Herceptin®), which inactivates the HER-2 protein. Another drug called lapatinib (Tykerb®) blocks the function of HER-2 and other selected proteins.

The identification of biomarkers can lead to novel treatment strategies or even identification of factors that cause cancer. An example of this process can be seen in chronic myeloid leukemia associated with the so-called Philadelphia chromosome. The Philadelphia chromosome is an abnormal chromosome that results from an exchange of genetic material between chromosomes 9 and 22. This exchange leads to the production of a protein called BCR-ABL that causes the uncontrolled growth of certain blood cells. The identification of this biomarker results in the classification of chronic myeloid leukemia into subtypes: Philadelphia chromosome positive or negative.

A drug has been developed that targets and inactivates the protein encoded by the Philadelphia chromosome. The medication is called imatinib mesylate (Gleevec®). Individuals with chronic myeloid leukemia who have the Philadelphia chromosome may be eligible for this medication, but those without the Philadelphia chromosome are not eligible because they would probably not benefit from it. Further pathology research indicated that Gleevec® could also inhibit a different abnormal protein that causes gastrointestinal stromal tumors (known as GIST). As a result, this medication is now used to treat GIST tumors that are positive for a protein called KIT. The use of Gleevec® is a concrete example of how tissue research can lead to a better understanding of the causes of cancer and development of a treatment that specifically targets the immediate cause. This is also an example of how many different kinds of scientists provided critical pieces of the puzzle that eventually resulted in the development of this drug.

As a result of research on the Philadelphia chromosome, we know that the protein it produces can cause blood cells to replicate. However, we still do not know why some individuals develop the Philadelphia chromosome and others do not. Further research may identify variables or factors that are consistently associated with the Philadelphia chromosome, which may lead to the identification of an environmental cause such as exposure to certain chemicals.

How Do Scientists Identify Novel Cancer Biomarkers?

Scientists use many different strategies to identify novel cancer biomarkers. In the past, these strategies focused on a single gene or protein. Thus, one test might be designed to detect the level of one protein. Many of these methods are still used today, as they often involve the analysis of easily-obtained bodily fluids such as blood or urine that are then analyzed using tests that are routine in many laboratories.

However, today, the identification of novel cancer biomarkers typically involves the assessment of multiple proteins or genes at once. In the search for biomarkers, this often involves assessment of numerous genes or their products in the same test. To identify the biomarkers, scientists may compare cancerous tissue and non-cancerous tissue to find genes that are differentially expressed in the two tissues. For example, a sample of cancerous colon tissue may express higher levels of certain genes than non-cancerous colon tissue. These genes may direct the cells to become cancerous. Conversely, the normal tissue may express genes that are absent from the cancerous tissue that help prevent the development of cancer. By using advanced techniques that can scan thousands of genes at once, scientists can identify a panel of candidate genes. These genes are then further analyzed to determine if one or more of them may be useful as cancer biomarkers. Increasingly, scientists are identifying multiple genes that together may be useful for determining prognosis or recurrence risk.

The following text describes three methods that are used by scientists today to identify novel cancer biomarkers: DNA microarrays, polymerase chain reaction (PCR), and reverse transcription PCR.

DNA Microarrays

DNA microarrays were developed to allow scientists to analyze the expression of many genes in a single experiment quickly and efficiently. The DNA microarray actually looks like thousands of tiny dots arranged in precise rows and columns. The basic principle behind microarrays is the specific binding of an mRNA molecule to the DNA template from which it originated. Each microarray contains many DNA samples so that the expression levels of hundreds or thousands of genes within a cell can be determined in parallel – this is referred to as a “high throughput” analysis. Using a computer, scientists can measure the amount of mRNA bound to each spot on the microarray, thereby providing a profile of gene expression. Gene expression refers to the translation of information encoded in a gene into protein or RNA. More information about microarrays and how they work can be found at the

National Center for Biotechnology Information (NCBI) website: <http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html>

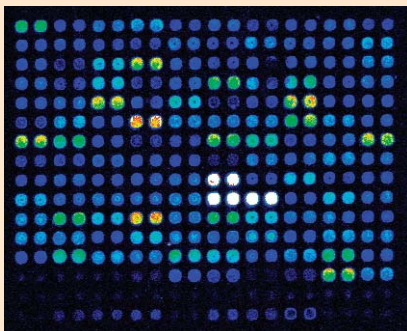


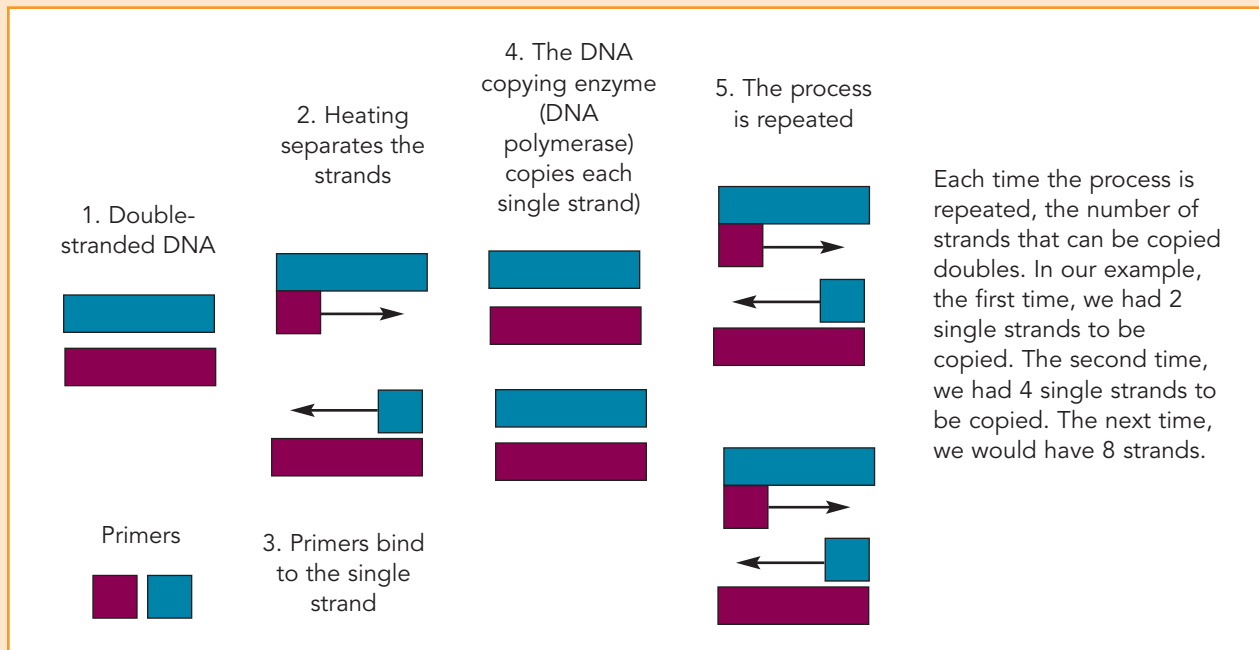
Image of a DNA microarray
(AKA: An Array “Heat Map”)

This graphic shows a DNA microarray. It consists of tiny dots that contain DNA probes. Some of these dots are lit up due to the presence of a fluorescent tag, indicating that the sample expressed a given gene. The different colors of the dots correspond to different levels of expression. Sometimes different colored dots such as red, black, and green are used in microarrays.

Polymerase Chain Reaction (PCR)

PCR is a laboratory method, typically used for research purposes, that amplifies small amounts of DNA so that it can be more easily detected and analyzed. In fact, it has been referred to as “xeroxing DNA.” The following figure shows the basic steps in PCR. PCR involves the use of primers or short sequences of nucleotides (subunits of DNA or RNA) that bind specifically to the DNA and signal the start of DNA copying. PCR is used with microarrays to copy the bits of DNA to be placed on the array. Today, a variation of PCR called multiplex PCR is gaining popularity. In multiplex PCR, multiple target sequences are amplified in one reaction by using many PCR-primer pairs.

Polymerase Chain Reaction



An additional image of the polymerase chain reaction can be viewed at the following website:
<http://www.britannica.com/eb/art-18071/The-three-step-process-of-the-polymerase-chain-reaction>.

Reverse Transcription-PCR

Reverse transcription (RT)-PCR is a technique that can be used to detect the expression of genes by making millions of copies of DNA from an RNA sequence. Regular PCR can be used to detect genes that are present but does not necessarily tell us whether they are expressed. This advantage of RT-PCR has made it a very useful addition to the techniques available for research and medicine.

RT-PCR detects RNA (ribonucleic acid) as opposed to DNA. RNA is the intermediate chemical that mediates the translation of DNA sequence into proteins. RNA is built like DNA—a series of four chemical letter bases—except that one of its bases is different: RNA uses a base called uracil (U) instead of the thymine (T) in DNA. We really do not know why this substitution takes place, but the A in DNA pairs exclusively with the U in RNA, just as it does with the T in DNA.

RT-PCR uses the same steps as PCR, but instead of DNA, the sample (e.g., from a tumor, blood, urine, etc.) contains a type of RNA. RT-PCR is finding many uses in cancer research and treatment. Because RT-PCR can detect even low levels of genes that are activated, it is being used to determine whether cancers have spread to distant regions.

Eventually, research into biomarkers will probably lead to an understanding of the causes of cancer and suggest ways to prevent it. In some cases, this has already happened. For instance, excessive sun exposure is known to cause mutations in a gene known as p53. This gene is involved in suppressing tumors and, when it is mutated, it can no longer perform its job. Certain types of skin cancer have been linked to excessive sun exposure and subsequent mutations in the p53 gene. Individuals are now advised to reduce their sun exposure and exposure to other sources of ultraviolet radiation or use sunscreen to avoid mutations in the p53 gene and the development of skin cancer.

Future Clinical Uses

In the future, the clinical uses of tumor biomarkers are likely to expand. More sensitive and specific biomarkers are likely to become available in the coming years that will enable clinicians to detect a wide array of cancers at earlier stages when they are responsive to treatment. The utility of these tests will depend on their validity, reliability, standardization, and cost-effectiveness.

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CHAPTER 5. ISSUES IN TISSUE PATHOLOGY RESEARCH

The goals of tissue pathology research are to gain a better understanding of disease, to devise more effective and tolerable treatments, to better predict who will be affected and why, and ultimately to prevent cancer. In order to progress as rapidly as possible toward these goals, researchers need to study tissue.

Need for Numerous Tissue Specimens

An important current issue in pathological tissue research is the need for large numbers of biospecimens. Many studies of tissue pathology are ongoing in the United States and throughout the world at any given time. These studies are diverse, involving multiple different cancer types and different scientific approaches. Some examples of studies that have been published within the last few years are listed in the following table. These represent only a few of the thousands of studies addressing tissue pathology in cancer that have been conducted and published since the year 2000. Today, additional research is attempting to determine how normal tissue progresses to cancerous tissue. Normal tissue specimens are needed for this research – a fact many people may overlook if not educated about the need.

Examples of Published Research Studies of Cancer Tissue Pathology

Study Citation (authors, title, journal, year, pages)	What the Study Found
Ishigami S, et al. Prognostic value of CCR7 expression in gastric cancer. <i>Hepatogastroenterology</i> . 2007;54(76):1025-8.	A protein called CCR7 found in preoperative gastric cancer tissue may predict lymph node metastasis of the cancer
Kawasaki K, et al. Expression of matrilysin (matrix metalloproteinase-7) in primary cutaneous and metastatic melanoma. <i>Br J Dermatol</i> . 2007;156(4):613-9.	A protein called matrilysin may be associated with melanoma progression and may enhance melanoma tumor cell invasion
Jha MK, et al. Variance of surgeons versus pathologists in staging of colorectal cancer. <i>Minerva Chir</i> . 2006;61(5):385-91.	In order to accurately stage colorectal cancer, a minimum of 9 lymph nodes must be examined by the pathologist
Han X, et al. HDM4 (HDMX) is widely expressed in adult pre-B acute lymphoblastic leukemia and is a potential therapeutic target. <i>Mod Pathol</i> . 2007;20(1):54-62.	A protein that regulates a tumor suppression gene may be a potential target for therapy of certain types of acute lymphoblastic leukemia
Paik T, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. <i>New Engl J Med</i> . 2004;351(27):2817-2826.	Describes the validation of a test that quantifies the likelihood of tumor recurrence in tamoxifen-treated patients with node-negative, estrogen-receptor-positive breast cancer

Because of the many studies being planned and in process, tissue specimens are needed continuously. The increased knowledge about human genes and the proteins they encode has led to an even greater need for tissue because researchers now have the potential to address questions that they could not before. Unfortunately, many areas of cancer research do not have adequate amounts of tissue. Several professional groups have identified the lack of access to pathological tissue specimens as a primary barrier to the development of cancer diagnostics, preventives, and therapies.

A related issue is that large numbers of tissue samples are needed in order to conduct robust studies that support strong conclusions. More studies are attempting to relate clinical findings such as long-term results of patients in a study (i.e., outcomes) with pathology findings such as an abnormal protein or the expression of many genes. This research depends on large numbers of biospecimens for analysis because of the variability associated with any human study. That is, humans do not live in a controlled environment and many factors can affect clinical outcome. Because we would not want to force everyone to live exactly the same way under the same conditions, the best way to combat variability is to have a large sample size.

Why Isn't There Enough Tissue For Biomedical Research

- Lack of knowledge about what tissue will be used for or why it is needed
- Lack of willingness to donate
- Physician resistance – they don't ask the patient
- Rare cancers or small tumors
- Lack of facility capabilities
- Lack of tissue from diverse populations

Given the importance of tissue to biomedical research that stands to benefit all of us, why isn't there enough tissue to go around? There are many possible reasons for this. First, some individuals simply lack knowledge about providing tissue for research. They may not understand the importance of donating tissue or even that there is an option to do so. They may also lack knowledge about what the tissue will be used for or may fear that their tissue may be misused. Often they are not asked by their physicians so the opportunity is missed. Characteristics of the cancer may also influence whether there is enough tissue for study. For instance, the tumors may be small or the cancer may be rare. Facility issues are also important in that some medical institutions may lack the capabilities needed to collect, store, and/or ship the tissue to the appropriate locations. Finally, in some instances, tissue is needed from diverse populations. This is particularly true for studies related to drug metabolism, as it is known that people of different races and ethnicities metabolize some drugs differently.

Advocates can play an important role in helping investigators obtain tissue for biomedical research. Many advocates have themselves donated tissue and can approach others as peers, not as physicians or researchers. Additionally, advocates often have the motivation and contacts to help design and implement tissue collection programs. Chapter 8 describes some examples of how advocates are helping to advance research by educating others and implementing tissue collection strategies.

Tissue Specimen Collection

Another important issue in pathological tissue research is the biospecimen collection procedure. The characteristics of the tissue specimen and its preparation can impact results. The collection procedures should be standardized and quality controlled in order to generate accurate and reproducible results. Special techniques are often required for collecting, storing, and shipping biospecimens for certain types of research such as genetic tests. Pathologists don't always know how to do this. Additionally, the type of fixative (a chemical used to preserve tissue in a stable state and prevent deterioration) used on the tissue may change its properties, which may preclude the identification of biomarkers.



Furthermore, it is important to ensure that tissue specimens for research purposes are only collected after the appropriate informed consent procedures are in place and after all diagnostic needs have been met.

The National Cancer Institute's National Biospecimen Network

The National Cancer Institute's National Biospecimen Network is a network devoted to the creation of a national tissue resource that supports the standardized and optimal collection, processing, storage, labeling, and distribution of tissue specimens. They are focusing on the following 5 areas:

1. Collection of large numbers of fresh/frozen cancer specimens
2. Accurate, highly standardized clinical labeling and associated data
3. Prompt and equitable specimen accessibility
4. Informatics platforms to facilitate sharing of data and results
5. Protection of patient privacy

The National Cancer Institute's National Biospecimen Network addresses many of the issues identified in this chapter. They recognize that studies of pathological specimens are essential to progress in cancer research.

Informed Consent

Informed consent procedures are essential to ensure that participants understand and agree to the collection and use of their tissue for research purposes. According to the Offices of Human Research Protection, informed consent must contain the following elements:

- A clear description of the operation of the biospecimen resource. This description could include details that may be of interest to human subjects (research participants), such as whether identifiable information will be maintained in the biospecimen resource and/or whether research results will be linked to the biospecimen.
- The conditions under which data and samples will be released to recipient-investigators.
- Procedures for protecting the privacy of human subjects (research participants) and confidentiality of data.
- Specific descriptions of the nature and purpose of the research.
- Where human genetic research is anticipated, information about the consequences of DNA typing.

The National Bioethics Advisory Commission has specified 5 fundamental elements of informed consent:

- Full disclosure of all anticipated relevant risks and benefits of the research. A participant has the right to know the future use planned for his or her tissues or medical information.
- The choice to participate must be voluntary.
- A clear statement of choice (an expressed decision) to participate in the research must be made by the potential participants.
- Assessment and assurance of the potential participant's competence to make a decision regarding whether to participate in the research.
- Statement that the potential participant comprehends the relevant risks and benefits.

The National Cancer Institute has also issued guidelines for informed consent documents pertaining to tissue specimens. According to these guidelines, tissue banks supported by the National Cancer Institute should use clear and specific informed consent language to ensure that people who contribute biospecimens and/or data for research purposes are fully informed that the research done with these biospecimens may help to develop products, tests, or discoveries, and that those products, tests, or discoveries may have commercial value and biospecimen contributors will not benefit financially from these discoveries. In fact, in the near future, it is likely that consent forms will be required to specify any financial benefit a participant may gain, as well as the financial rights they give up. In most cases, this involves a statement indicating that, if a product gets developed based on the study, participants don't get any money from it. In other words, participants will not be paid royalties or other money as a result of product development.

Tissue Specimen Storage

Once tissue has been collected, it must be appropriately stored so that it remains viable for research. If tissue is not stored adequately, it will degrade or deteriorate so that it is not useful for research. The storage and handling of biospecimens is expensive and requires a great deal of expertise. For these reasons, centralized tissue storage banks have been established. Issues still remain, however, such as whether, and under what conditions, the tissue samples can be moved.

Different Types of Tissue Banks and Resources		
Type of Tissue Bank or Resource	Definition	Example
Traditional tissue bank	Collection and storage of specimens and associated data at a single central facility	Radiation Therapy Oncology Group, San Francisco, CA
Virtual tissue bank	Specimens collected and stored locally with the associated specimen data centralized. Requests for specimens are handled through a central coordinating office	Cooperative Breast Cancer Tissue Resource
Prospective tissue procurement services	Collection of specimens to meet investigator requests. In this model, most specimens (except for rare specimens) are stored only for limited time periods until they can be distributed to the investigators who request them	Cooperative Human Tissue Network

From: National Cancer Institute Cancer Diagnosis Program. How to establish and manage a tissue bank or other biospecimen resource.

Tissue Identification

Every tissue sample must be adequately documented and labeled, but de-identified as per the informed consent and participant privacy requirements. One method for doing this is to use a bar code that links to information about the sample such as the tissue type, collection method, collection date, and other relevant information.

Tissue Shipping

Tissue must be shipped according to standard specifications in order to ensure its continued viability for research. For instance, if tissue accidentally thaws before reaching its destination, it may be rendered useless for research. The exact shipping conditions depend on a variety of factors such as the type of sample and the season. The National Cancer Institute has issued guidelines for shipping that are elaborated later in this chapter.

Tissue Distribution and Access

Another concern with pathological tissue is distribution and access. For instance, who should be allowed to use the tissue samples in research? Should the patient be involved in determining this? Some pathologists will not share biospecimens with other researchers for various reasons such as loss of control over the tissue. What can be done to promote distribution and access to tissue for well-designed research projects? The tissue sample is a finite quantity. Investigators may take a punch or slice from a small block of tumor tissue for a study, but this can only be done a limited number of times before the tissue is simply used up. Therefore, decisions must be made about the studies for which the tissue should be used.

Best Practices for Biospecimen Resources

The National Cancer Institute has issued guidelines for biospecimen resources. These guidelines specify general principles related to the collection, processing, storage, retrieval, and dissemination. Many of the specific details of these procedures depend on the tissue being collected and the goals of the research. However, a number of common practices have been identified and are briefly summarized in the following text. The full text is available on the National Cancer Institute's website listed at the end of this chapter.

Determining Which Biospecimens to Collect

This is based on the defined purpose of each biospecimen for specific types of research. Biospecimens are collected from populations in accordance with the scientific goals of the research.

Biospecimen Collection and Processing

All data relevant and necessary to research goals are recorded by biospecimen resources. The amount of time elapsed during collection is recorded; collection time should be minimized for solid tissue specimens but may not be as critical for other types of biospecimens such as blood.

Biospecimen Resource Personnel

Personnel involved in the management of biospecimens should be aware of the purpose and goals of the biospecimen resource. Personnel must be well qualified and trained to adhere to standard operating procedures.

Biospecimen Storage

Standardized protocols must be applied to ensure biospecimen quality. Biospecimens are stored in a stabilized state and not thawed and refrozen unnecessarily. Storage temperature is based on type of biospecimen, length of storage, biomolecules of interest, and the need for preserving viable cells. Storage containers are selected based on analytical goals. Each biospecimen storage container has a unique identifier or combination of identifiers that is clear and can endure storage. All other relevant information is tied to this identifier, keeping in mind participant confidentiality, security and informed consent requirements. Security systems continuously monitor the function of storage equipment.

Shipping Samples

Samples must be retrieved from storage according to biospecimen resource standard operating procedures in order to maintain quality. Shipping temperature must take into account shipping time, distance, climate, season, method of transportation, regulations, type of samples, and intended use of the samples. Before shipping, the biospecimen resource notifies a recipient to confirm that sample can be accepted and properly stored. Regulatory guidelines related to national or international shipping, as well as occupational safety and health, must be adhered to. Personnel responsible for shipping must be appropriately trained.



Ownership of the Tissue

The ownership of tissue specimens is still being debated. Questions in this area include: Who owns the tissue – the hospital or the patient? Can patients continue to determine what is done with their biospecimens once they have provided them? Several notable court cases have involved these issues. The law is different with regard to diagnostic biospecimens as opposed to research biospecimens. In several states, the hospitals own tissue removed for diagnostic purposes and have been held legally responsible for its proper handling and storage. In one case, the courts determined that research participants have a continuing interest in their biospecimens, including the right to require that the biospecimens no longer be used for research. In another case, the courts determined that tissue specimens are the property of patients that can be given as gifts. This procedure transfers ownership rights from a patient to a research institution if that is the intent of the patient. However, legal and regulatory standards still vary among different groups and states, and there is an overall lack of consensus regarding the ownership of tissue specimens.

Custodianship is a term that comes up repeatedly in considering the ownership of tissue specimens. In this context, a custodian is any person or organization in possession of a tissue specimen, often a pathologist or pathology department. Custodians have responsibility as specified in the informed consent to fulfill the research participant's intentions. However, occasionally, custodians do not adhere to their responsibilities. In the past, some custodians have assumed ownership of the tissue and interfered with the research purpose, failed to fulfill the wishes of research participants, and ignored the informed consent. These actions threaten the entire process of tissue provision for research and are therefore important to guard against.

Need for Additional Research Studies and Follow-Through

For many cancers, research is not proceeding as quickly as hoped. An example of this is pancreatic cancer. Pancreatic cancer spreads rapidly and produces few symptoms until the disease reaches the late stages. Furthermore, it is resistant to chemotherapies that often work for other cancers. A recent think tank concluded that research into the molecular causes and effective treatments for pancreatic cancer is progressing too slowly and examined ways to speed the process. Development of a tissue bank was identified as a primary goal of this group.

Another important issue in pathological tissue research is the follow-through with committed studies. Clinical studies of new medications or combinations of medications often include a tissue research component. That is, as part of the study, participants provide tissue specimens to be used in relating clinical outcomes to the pathology of the tissue. For instance, researchers may ask the following types of questions: Are the levels of protein X in participants' tumor cells related to long-term survival? Is remission of the cancer related to the expression of genes X, Y, and Z? Is the pattern of chromatin in the cancer cells related to response to chemotherapy, prognosis, or cancer recurrence? Such questions are increasingly being asked as part of large clinical trials conducted by cancer cooperative groups. Such questions are often referred to as correlative science. A correlation is the tendency of two variables to co-occur. This can be a positive correlation: as one variable increases, so does another,

as in the case of increased smoking leading to an increased chance of lung cancer. Or it can be a negative correlation: as one variable increases, another decreases, as in the case of increased levels of physical fitness associated with lower blood pressure. The correlation of interest in correlative science is the relationship between some pathological feature of the tissue and clinical outcome.

Despite the commitment on the part of researchers to conduct these pathology investigations, many projects stall or are never completed. There is a pressing need to ensure that the investigators follow through with pathology projects to which they have committed. This is an area in which advocates may have a profound effect. Advocates can bring a sense of urgency to these studies, reminding research groups of the human component to their research and the many individuals with current and future cancers who stand to benefit from their findings.

Ensuring Execution of Commitments

Study Follow-Through

It is important to ensure that investigators follow through with studies to which they have committed. In some cases, participants have provided tissue for specific studies that investigators and institutions have agreed to conduct. However, for a variety of reasons, the study may be stalled. Given the potential importance of these studies, indefinite stalling is not acceptable. However, sometimes studies are halted for very good reasons and should not proceed. The main issue is whether or not investigators have a responsibility to those who have donated tissue. By bringing a sense of urgency to the table and reviewing the prior commitments with investigators and administrators, advocates may be able to critically influence research progress.

Adherence to Protocol Commitments

It is also critical to ensure that investigational sites actually provide the tissue that they agreed to provide. In some protocols, individual study sites agree to send the tissue to a central tissue bank for analysis or storage. Despite their commitment, some sites do not do this, and in effect renege on their commitments. Advocates can be influential here by reminding the institution of its commitment and/or exploring the reasons that the institution no longer elects to comply with the protocol.

Spotlight on Pathology Issues in Breast Cancer

A Consensus Group for Susan G. Komen for the Cure, a non-profit organization devoted to curing breast cancer, has published a recent article in the *Breast Journal*. This article identified concerns related to the quality and practice of breast cancer pathology. Pathology issues were identified through a literature review and interviews conducted in 2005-2006 with experts in oncology, breast pathology, surgery, and radiology. The interviewees practiced in community, academic, and cooperative group settings.

The article identified 4 main areas of concern in pathology that have a direct impact on the quality of care breast cancer patients receive in the United States:

- Accuracy of breast pathology diagnostics
- Effects of current health insurance and reimbursement policies on patients who are evaluated for a possible breast cancer diagnosis
- Substantial decrease in tissue banking participation, particularly during a time of rapid advances in biologically correlated clinical science
- Roles of various organizations in ensuring that breast pathology practices meet the highest possible standards

The article identified several other areas of concern in pathology, including the lack of integration of pathologists in the clinical care team, inadequate compensation for the amount of work required to thoroughly analyze specimens, potential loss in translational research as a result of medical privacy regulations, and the lack of mandatory uniform pathology practice standards without any way to measure the degree of variation or to remedy it.

Perkins C, Balma D, Garcia R; the Members of the Consensus Group. *Why Current Breast Pathology Practices Must Be Evaluated*. A Susan G. Komen for the Cure White Paper: June 2006. *Breast J.* 2007;13(5):443-447.

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CHAPTER 6. ETHICAL CONSIDERATIONS

The previous chapter included a discussion of informed consent because of its central importance in the process of collecting and storing tissues. Indeed, informed consent is one of the key ethical considerations in all research involving human subjects. However, additional ethical considerations arise whenever researchers seek to obtain tissue specimens that are important for advocates to consider. Some of these are specific to genetic research because tissue research in cancer is increasingly focusing on the study of genes. Over the past decade, scientific knowledge about human genes has increased immensely as a result of the Human Genome Project. Scientists now know the location of all the human genes and the order of the letters of the genetic alphabet that make up those genes. Scientists are now trying to figure out the functions of all of these genes and how they work together in health and disease.

Therefore, many of the ethical considerations involving tissue research were anticipated by the Human Genome Project's program devoted to studying these issues: the ethical, legal, and social implications (ELSI) research program. In addition to the ELSI program, many of the ethical considerations are discussed in the National Cancer Institute's National Biospecimen Network Blueprint and the work of the National Bioethics Advisory Commission – all of which are listed at the end of this chapter. Although some of the issues remain the source of ongoing regulatory and legal discussion, advocates may want to be mindful of them.

Identifiability of Biospecimens

In general, the more a biospecimen can be linked to (or identified with) a specific person the more valuable the genetic information contained in it will be to researchers. This means that the risks to individual privacy and confidentiality are also heightened. Advocates should be aware of this balancing issue. Studies that only use completely unidentifiable tissues (because they were collected without any identifying information) will ensure patient confidentiality, but may slow the pace of research, whereas studies that use completely identifiable tissues (because names, medical history and other information is linked to the sample) will provide more valuable data to researchers but increase the risk of unintended leak of private information to third parties.

Impact on Privacy and Confidentiality

Among the ongoing concerns about providing tissue specimens for research use is the possibility that individuals and organizations who do not have a “right to know” may get access to information and use it against the tissue contributor in some way. Some are concerned that health or life insurance companies, employers and others may inappropriately discriminate against a person on the basis of genetic information revealed in a tissue specimen. While, thankfully, cases of such discrimination are rare, advocates should be aware that the threat to individual privacy and confidentiality is real and that standards now exist for ensuring the protection of confidential information in research that should be followed.



Access to Research Results

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifies that individuals have access to their medical records and other types of personal health information under most conditions. Participants may also want information about research results involving their tissues. Additionally, it is possible that pathologists who are examining the tissue for use in a research study may discover something about the biospecimen that could be medically significant for the individual, such as the presence of a biomarker that was missed in the initial tests. While each research study may be considered on its own merit, current thinking is that tissue contributors should not expect that they will receive individual research results from studies on their tissue.

Conflicts of Interest, Commercialization and Other Financial Considerations

Research on tissues is becoming an important business opportunity. As such, the collection, storage and research use of biospecimens will inevitably raise concerns about access and purchase of biospecimens, and the nature of the relationship between researchers and their research sponsors. For example, whenever a researcher stands to gain financially from their research on collected biospecimens, patients' advocates should be aware of these arrangements and be prepared to advise patients accordingly.

Informed consents should also state if the tissue is to be sold for cost recovery or profit. In some cases, tissue banks sell the tissue to cover the costs of their operation. This is referred to as cost recovery. Tissue sale for cost recovery does not involve monetary profit. Other tissue banks, however, sell tissue for monetary profit. Individuals should understand whether the tissue they are providing is to be sold for cost recovery or profit and should be agreeable to the terms before signing the informed consent.

The ELSI program has identified numerous questions related to human genome research that fall into a number of categories, as shown in the following table.

Ethical Issues Related to Human Genome Research as Identified by the ELSI Program	
Issue	Example
Fairness in the use of genetic information by insurers, employers, courts, schools, adoption agencies, and the military, among others	<i>Who should have access to personal genetic information, and how will it be used?</i>
Privacy and confidentiality of genetic information	<i>Who owns and controls genetic information?</i>
Psychological impact and stigmatization due to an individual's genetic differences	<i>How does personal genetic information affect an individual and society's perceptions of that individual? How does genomic information affect members of minority communities?</i>
Reproductive issues including adequate informed consent for complex and potentially controversial procedures, use of genetic information in reproductive decision making, and reproductive rights	<i>Do healthcare personnel properly counsel parents about the risks and limitations of genetic technology? How reliable and useful is fetal genetic testing? What are the larger societal issues raised by new reproductive technologies?</i>
Clinical issues including the education of doctors and other health service providers, patients, and the general public in genetic capabilities, scientific limitations, and social risks; and implementation of standards and quality-control measures in testing procedures	<i>How will genetic tests be evaluated and regulated for accuracy, reliability, and utility? (Currently, there is little regulation at the federal level.) How do we prepare healthcare professionals for the new genetics? How do we prepare the public to make informed choices? How do we as a society balance current scientific limitations and social risk with long-term benefits?</i>
Uncertainties associated with gene tests for susceptibilities and complex conditions (e.g., heart disease) linked to multiple genes and gene-environment interactions	<i>Should testing be performed when no treatment is available? Should parents have the right to have their minor children tested for adult-onset diseases? Are genetic tests reliable and interpretable by the medical community?</i>
Conceptual and philosophical implications regarding human responsibility, free will vs genetic determinism, and concepts of health and disease	<i>Do people's genes make them behave in a particular way? Can people always control their behavior? What is considered acceptable diversity? Where is the line between medical treatment and enhancement?</i>
Health and environmental issues concerning genetically modified foods (GM) and microbes	<i>Are GM foods and other products safe to humans and the environment? How will these technologies affect developing nations' dependence on the West?</i>
Commercialization of products including property rights (patents, copyrights, and trade secrets) and accessibility of data and materials	<i>Who owns genes and other pieces of DNA? Will patenting DNA sequences limit their accessibility and development into useful products?</i>

From: U.S. Department of Energy Office of Science, Office of Biological and Environmental Research, Human Genome Program. Ethical, Legal, and Social Issues.

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CHAPTER 7. QUESTIONS TO ASK

Advocates are often in a position to raise questions about pathology research. In specific situations, it may be important to seek answers to the following questions prior to the initiation of a study.

Clinical Pathology

1. Has the proposed pathological test been validated?
2. Is the test reliable?
3. Does the test have clinical utility?
4. Is the test standardized?
5. Who will be conducting the test? If different laboratories, what procedures are in place to ensure quality control and standardization?

Need for Numerous Tissue Specimens

1. Is there an opportunity in this study to obtain tissue specimens for research?
2. Is there an opportunity to include correlative science (correlate long-term clinical results with tissue pathology)?
3. Are any steps being taken to educate participants about the need for tissue specimens and the opportunities/procedures for tissue provision?

Tissue Specimen Collection

1. Are all participating healthcare professionals adequately trained to collect the types of biospecimens needed for this study? If the biospecimens may be used for future studies, are the professionals trained in collection procedures that would permit biospecimens to be used for gene-based research?
2. Are there standardized procedures in place for collecting the biospecimens?

Informed Consent

1. Does the informed consent document meet the following requirements?
 - a). A clear description of the operation of the biospecimen resource and any identifiable information.
 - b). The conditions under which data and samples will be released to recipient-investigators.
 - c). Procedures for protecting the privacy of human subjects and confidentiality of data.
 - d). Specific descriptions of the nature and purpose of the research.
 - e). Where human genetic research is anticipated, information about the consequences of DNA typing.
2. Should different levels of participation be included? (e.g., tissue to be used only for the current study, tissue to be used for any study of certain cancer types, tissue to be used for any study that requires pathological tissue, etc.)

Tissue Specimen Storage

1. How and where will the tissue specimens be stored?
2. Who is in charge of the storage?
3. How can we ensure that the tissue specimens will remain viable over the course of storage?

Tissue Distribution and Access

1. If there is tissue left over after the research needs who will be allowed to use it in the future, if anyone? Does the consent form specify that the tissue should only be used in one specific study or can it be used in other studies?
2. What is the process for sharing biospecimens among researchers?

Ownership of the Tissue

1. Who owns the tissue being used in this study?
2. Do the participants continue to have a say in what is done with the biospecimens once they have provided them?

Need for Follow-Through

1. Are there set timelines for completion of the pathological research?
2. What procedures are in place to ensure that the pathological research component of the study gets completed?
3. Are there enough researchers involved to get the pathological research completed by the set date?

General Questions From the National Institutes of Health and National Cancer Institute

Custodianship and Ownership Issues in Biospecimen Research

1. What type of information regarding ownership and custodianship of biospecimens should be provided to research participants through the informed consent form? Should there be clear informed consent language to distinguish between control of biospecimens and associated data, and control of information generated through research on biospecimens?
2. Can Principal Investigators and institutions efficiently navigate the State-to-State discrepancies in regulations governing biospecimens, or should broad Federal preemption of State laws be used to ensure greater legal consistency?
3. What must be told to potential participants about their rights to withdraw from research and the consequences of discontinuing participation? What actions must custodians take when participants withdraw from research?
4. With respect to biospecimens, what are the custodial rights and roles and responsibilities of host institutions, managers of biospecimen resources, Principal Investigators, and research participants? Should different levels of roles and responsibilities be established?
5. Can institutions distribute biospecimens as they see fit or must they adhere solely to the uses described in the informed consent form?
6. What are the best policies for governing the disposition of biospecimens and associated data when the funding period ends or the Principal Investigator transfers to another institution or retires? What must participants be told about what will happen to the research and the biospecimens under these circumstances?

A variety of organizations host websites that contain educational material relevant to tissue pathology and research. These organizations may be useful sources for identifying important issues and stimulating the development of informed questions. Several of these organizations are described in the following text.

Genetic Alliance

Genetic Alliance is a coalition of advocacy organizations and individuals that serve individuals affected by genetic conditions. This organization offers numerous training opportunities and tools for advocates. One such tool is entitled *The Interactive Guide to Advocacy* – a manual that “covers every aspect of founding and growing an advocacy organization – from fundraising to detailed explanation of issues, skills, and elements of creating a registry and samples repository.” More information about the Genetic Alliance is available at: www.geneticalliance.org.

Cancer Biomedical Informatics Grid™ (caBIG™)

The Cancer Biomedical Informatics Grid™ (caBIG™) is a National Cancer Institute initiative designed to accelerate research discoveries and improve patient outcomes by linking the interested parties, including patients, physicians, and researchers. caBIG™ has developed many resources that may be useful to advocates in helping to stimulate and formulate questions about tissue research. Many of these materials are available on their website: <https://cabig.nci.nih.gov/>.

Sources

Prostate SPORE National Biospecimen Network Pilot. NBN blueprint. Available at: http://prostatenbnpilot.nci.nih.gov/blue_full1.asp. Accessed September 5, 2007.

National Institutes of Health. National Cancer Institute. Custodianship and ownership issues in biospecimen research. A workshop background paper. Rockville, Maryland October 4–5, 2007.

CHAPTER 8. ADVOCATES AND TISSUE PATHOLOGY RESEARCH

Many advocates have had direct experience with tissue pathology by providing samples of their own tissue for diagnosis. This gives advocates a personal perspective on how tissue is collected and the importance of gaining accurate, thorough information from the pathologist that is informed by sound scientific research. Some advocates have participated in clinical trials involving tissue pathology research, resulting in yet another perspective. Additionally, each advocate has a history of unique experiences that helps shape individual views about tissue pathology research and plays a role in determining the issues that he or she deems to be important.

The following section describes some of the critical issues in tissue pathology research identified through interviews with advocates who are active participants in the field. Most of these issues can be grouped under the central theme of “giving back.” That is, researchers take tissue samples from individuals. Many advocates would like to see the research community give something back to the people who provided the samples.

However, not all advocates hold this perspective. Some advocates believe that tissue provision should be done for the general good of science rather than with the expectation of any gain or return. Thus, not all advocates believe that that people who provide tissue for research should expect to get something back.

Giving Back the Tissue

In some cases, individuals who provide tissue for diagnosis or research would like that tissue physically returned to them. The reason for seeking tissue return may be personal (e.g., “It’s my tissue and I want it returned”). In other cases, the reason is cultural. For instance, many Native Americans believe that, upon death, the body should be buried as a whole. A body missing blood, an organ, or a piece of tissue is not considered whole. Thus, it is important that there is a mechanism in place for investigators to keep track of the tissue provided so that it can be returned to the individual upon request.

In general, researchers do not think about the possibility of physically returning the tissue. They may not be aware of Native American customs and beliefs and, based on their own experiences, may not understand why an individual would want the tissue back for personal reasons. In cases where the tissue was used for diagnosis, the institution at which the sample was collected may fear legal repercussions. For instance, if the tissue sample were taken to another pathologist and a different diagnosis rendered, the institution may be sued.

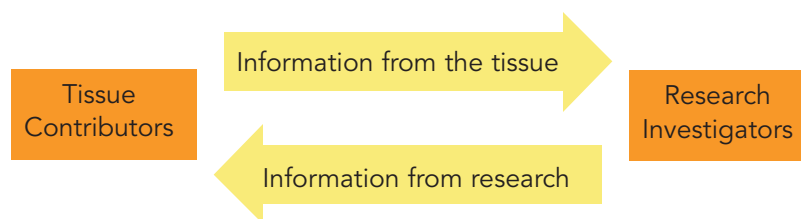
Today, tissue is rarely returned to individuals who have provided it for diagnosis or research, and many do not want the tissue back. The tissue is typically sliced and placed on a slide and may contain dyes or other chemicals. Some individuals would not relish the idea of having a slide such as this come to them in their mailbox. However, it is critical that the medical and scientific communities realize that not all individuals feel the same way and that there may be compelling personal and cultural reasons for wanting tissue returned. By recognizing and honoring these requests, the medical and scientific communities demonstrate respect for the tissue and the people who provided it.

Tissue return represents a challenge for advocates because the mechanisms for tracking tissue and sending it back to individuals who provided it are not routine. Some advocates are trying to initiate a dialog with the medical and scientific communities to alert them of the need to return tissue upon request and to devise procedures through which this can be done.

Giving Back Information

For many advocates, a central issue in tissue pathology is the need for investigators to give information back to those who provided samples. This information may take several forms.

Bidirectional flow of tissue information. Many advocates envision a bidirectional flow of information in which information contained within the tissue is transferred to researchers and researchers provide information back to the tissue contributors



General (population) information

Those who provide tissue for research frequently want to know the results of studies to which they contributed. In fact, the communication of results is a basic tenet of science, designed to permit replication of experiments and, conversely, prevent unnecessary repetition of previously completed work. This allows science to move forward and build on previous findings.

The communication of information about the general research study population usually involves summaries of the data as opposed to findings from individual participants. These summaries often take the form of averages or ranges. General population results might be communicated back to participants in many ways, including newsletters or publications in scientific journals, although the latter rarely gets to patients. This type of communication serves to strengthen the public trust in tissue research and may increase participation in research studies. However, one challenge with the communication of results back to patients is cost. Typically, the economic costs of transmitting this information are not written into the study budget, raising the issue of who is to pay for this communication. Cost may be even more of an issue when tissue is obtained from individuals scattered across the nation. Additionally, someone must have the time set aside for this communication. Advocates may be able to help in this regard, seeking out effective and economical modes of communication.

It is usual practice in science for investigators to communicate results of their studies in medical or scientific journals. However, most study participants probably do not read the scientific journals in which the results would be published. Additionally, some scientists do not publish their work if they get negative results – that is, if they did not find a link between the items they were looking at (e.g., cancer and playing a musical instrument). Thus, advocates

may be challenged with asking the researchers to communicate the results in a newsletter to be sent to participants and ensuring the publication of negative findings.

Individual information

Although it is common for researchers to communicate the general population results from their studies to the research/medical community, it is not common for them to communicate individual information. However, important information that could help an individual or his/her family is not withheld. In most cases, the premature communication of information may be more detrimental than helpful. Thus, the communication of individual information is not necessarily desirable under all circumstances, although there may be specific instances in which this is beneficial.

Given the legal and ethical issues, it is considered difficult to communicate individual results back to the person who provided the tissue. However, advocates and other groups are exploring ways in which this could be done. It would be important to make sure that the results communicated back to individual participants are meaningful and significant and to ensure that considerate, predictable, and consistent methods are used for contacting participants. It should also be possible for participants to decline to receive information on their specific findings. Despite these challenges, the prospect of obtaining individual results may serve as a powerful motivator for research participation and may serve to further strengthen the public trust in tissue research. However, an additional challenge is the effect of this communication on patients who may have participated in the study, but were assigned to the less beneficial treatment group. Will these patients be depressed or angry? These emotional considerations make the communication of individual results a controversial issue.

It is also critical to note here that research laboratories are not the same as clinical laboratories and do not necessarily follow the same procedures. Basic research laboratories handle samples in different ways than do clinical research laboratories. The latter must be CLIA-approved, whereas basic laboratories have no such requirements. Investigators and other groups are actively debating if, when, and how information obtained in basic research laboratories could and should be communicated back to patients. Some have argued that basic laboratories may need to obtain CLIA approval for this to happen. Relevant dialog on this issue can be found on the *Science* magazine website (www.sciencemag.org) at the following specific link (<http://www.sciencemag.org/cgi/eletters/316/5826/836#10205>).

Another important issue in considering the communication of individual results is the concern over premature release of information. It is critical that information not be released to patients or the general public before it is validated. An example of premature release of information occurred with several genes that have been linked to an increased risk of breast cancer, BRCA1 and BRCA2. When the information about these genes was first released, the risk was believed to be higher than later studies showed it to be. Because the estimated risk was thought to be higher, some women underwent prophylactic mastectomies to lower their personal risk. Later studies found significant increase in life expectancy for young women, but not women over age 60,

who had these mutations and underwent prophylactic mastectomies (see references by Hartmann, Meijers-Heijboer, and Schrag at the end of this chapter). A related concern is the premature release of results, which may or may not be borne out as they mature. Premature results may give false or incomplete answers to the question being asked, resulting in erroneous or misleading conclusions.

Additionally, in order for study results to be published in reputable scientific journals, they must undergo peer review. This process involves critical evaluation of the data and conclusions by multiple scientists who are unrelated to the study, which increases confidence in the findings.

Specific group information

A related issue is the need for direct follow up with study participants if the research involves a specific group or population. An example of this is The Nun Study, which involves 678 nuns from the School Sisters of Notre Dame religious congregation between 75 and 106 years old. This has turned out to be a landmark study on aging, providing much useful and previously unknown information. The investigator has followed up with the congregation of nuns, who have been honored on several occasions for their participation.

For each specific population, there may be an appropriate venue at which investigators may want to consider presenting research results. That is, results could be presented where the people whom they are trying to reach are located. For instance, results from studies with Native Americans could be offered for presentation in conjunction with Tribal Council meetings. In presenting results related to specific groups at relevant venues, investigators will help to link the circle of research back to the participants and perhaps stimulate interest in future participation. In some cases, the investigators themselves may not think to communicate in this way, or may consider it burdensome, whereas other investigators may initiate this type of communication themselves.

Future information: Saving tissue for potential future clinical benefit

Often, the only time individuals provide tissue for diagnostic or research purposes is at a single physician visit or surgery whose purpose is to determine whether they have cancer or another disease. This can be an extremely stressful time, when the primary focus is on a potentially life threatening condition and how it will affect one's life and family. In this situation, most people likely do not think to ask their healthcare provider to save some of their tissue for potential future use.

However, it is possible that having such tissue could provide future benefits to the person or his/her family. For instance, investigators may discover that cancers expressing certain genes may be more likely to recur than those that do not express the genes. A person's saved tissue could then be tested for those genes to determine the likelihood of recurrence. In fact, paraffin blocks of tissue are routinely saved, but the problem is often that investigators don't have permission to use them.

Some tissue banks (e.g., the Cancer and Leukemia Group B [CALGB] tissue bank) do have a process for saving a portion of a person's tissue for possible future clinical benefit. Many advocates believe that this should be standard

practice for all tissue banks and are working toward that end. However, tissue taken at a diagnostic visit is rarely saved for future use and possible future clinical benefit. Advocates are helping educate individuals about these issues before they are faced with providing tissue for diagnosis. Given that this is the only time many people provide tissue, such education is critically important. Additionally, healthcare providers are not always aware of, or interested in, the options surrounding tissue contribution, which is another challenge for advocates.

Giving Back: Indirect Monetary Benefits

As noted in chapter 5, consent forms often specify any financial benefit a participant may gain or the financial rights they give up, when donating their tissue. This usually takes the form of a statement noting that the person who contributes tissue doesn't get any money from products or discoveries that are made from research involving their tissue. In many cases, those who provide tissue for research do it so that they or others might benefit from scientific discoveries and do not expect direct financial benefits.

However, some advocates have pointed out other situations in which tissue contributors should not give up financial rights. For instance, a woman may have been diagnosed with skin cancer and may elect to contribute tissue that leads to the development of a clinical diagnostic test. If she goes back to her healthcare provider in 5 years to determine whether her cancer has returned, she should probably not be charged \$3000 for the test that her tissue helped develop.

In the realm of tissue research, other financial situations are likely to arise in which tissue contributors may not want to give up rights. For this reason, it is important for tissue contributors to know exactly what they are signing in their consent forms. For instance, it is important for tissue contributors to know if their tissue may be sold to researchers. Tissue is often sold by tissue banks for the purpose of cost recovery; that is, tissue banks are allowed to recover costs for their maintenance and operations. Tissue sold for cost-recovery, by definition, does not involve monetary profit. On the other hand, some tissue banks are for-profit institutions that sell tissue for monetary gain. Tissue contributors are typically not paid for providing their tissue for research. It is critical that individuals understand what they are signing in their consent forms to be sure that they are agreeable to the terms related to cost-recovery or monetary profit from their tissue.

Tissue Banks

Tissue banks and their operation are a critical issue for many advocates. Often, investigators who collect tissue for a particular research project feel intense ownership of the biospecimens. They may be unwilling to share tissue with others or to allow advocates to have a say in what is done with the tissue. Researchers argue that to comply with all of the requests of advocates would be extremely time-consuming and would slow research.

These observations have led to the establishment of a number of national tissue banks such as the Susan G. Komen for the Cure Tissue Bank and the CALGB tissue bank. Some advocates have even formed their own tissue

banks in order to protect the rights of those who provide tissue for research and to ensure that they have a say in what is done with that tissue. An example is the Inflammatory Breast Cancer Foundation's Biobank (<http://www.ibcresearch.org/diagnosed/biobank/>). Other advocates are working with the National Cancer Institute to develop best practice standards for tissue banks that take into account some of the concerns outlined in this chapter.

Consent and Honoring Participant Choices

Another important issue is consent and the honoring of participant choices on consent forms for research projects. When individuals sign consent forms indicating that they want their tissue to be used for selected projects, the researchers should use the tissue only for those projects. Similarly, by signing the form, individuals are essentially saying that they expect their tissue to be used for those studies and not to sit unused in a repository.

In order to document whether a person's choices have been followed, institutions need to be audited. Some advocates are working to ensure this adherence by requiring "best practices" audits.

Narrow vs. Broad Consent

While some are concerned that tissue samples be used only for projects specified by the individual who provided the tissue, others are concerned about excessive restrictions. That is, some advocates argue that placing numerous restrictions on how the tissue is used may slow scientific progress. They argue that restrictions may be difficult to execute and may place an unnecessary burden on researchers, potentially hindering scientific advances. The risks of broadening the research to which individuals consent may often be associated with minimal or no risk compared with a larger potential for benefit.

This view does not imply that those who provide tissue should consent to anything and everything. Rather, it suggests that not all people who provide tissue feel the same way about it. Some individuals are not interested in restricting research uses of their tissue, provided that basic safeguards are followed. Optimally, the system of tissue banking and research would be able to accommodate those with different views about the uses of their tissue. One approach that has been used is a checklist, whereby individuals can mark one of several options related to use of their tissue, including "only for research specified," "any research related to my disease," or "any research for any disease."

Importance of Educating Individuals Before They Are Diagnosed With Disease

As noted previously, the only time many people provide tissue samples is at diagnosis. This is not an optimal forum to discuss contributing additional tissue for research or deciding which organization (e.g., which tissue bank, which research study) should receive the tissue. For these reasons, many advocates believe it is critical to educate the public prior to a diagnosis situation. One group that is attempting to provide this type of education is the Arizona Myeloma Network, as described later in this chapter.

People who are educated in this way may be more likely to provide a bit of extra tissue when they are undergoing procedures for diagnosis. They may also be more likely to select a treatment center that will treat their tissue as a valuable resource. Asking individuals to consider providing extra tissue at diagnosis may also have the advantage of reducing the current tissue shortage. Some advocates view this preparation much in the same way our society prepares for fires and other unexpected adversities. An additional challenge in this area is to ensure the participation of oncologists, many of whom are not researchers and are not necessarily interested in obtaining tissue for another person's research, or for some intangible future benefit to society.

Need for a Well-Organized System for Tissue Contribution

For some advocates, an overriding issue in tissue research is the need for a well-organized system for those willing to contribute their tissue. Included in this is a need for the development of best-practices procedures to which all tissue banks and researchers adhere. This adherence would minimize inaccurate results, enhance public confidence, and lead to more rapid realization of clinical benefits.

The National Cancer Institute is in the process of developing best practice standards for biospecimens. More information about this can be found on the National Cancer Institute's website at <http://biospecimens.cancer.gov/practices/>.

Importance of Translational Research

Another important issue for many advocates is the need for translational research. Translational research is research that has direct clinical relevance and often involves an attempt to translate basic science into clinical practice. Although many basic science discoveries are being made, there is often a long time lag before patients realize any benefits. There is an urgent need to move the results of basic laboratory research into the clinical realm more quickly, without sacrificing validity, clinical utility, safety, or efficacy. Many advocates want to ensure that some tissue is being used for translational research and are working toward that goal.

These issues emerged from interviews/discussions with the following advocates:

1. Celeste Whitewolf, JD, Director, Native People's Circle of Hope Advocate
2. Ginny Mason, RN, Advocate, Inflammatory Breast Cancer Research Foundation
3. Karl Schwartz, President and Co-founder, Patients Against Lymphoma
4. Mary Lou Smith, Co-founder, Research Advocacy Network
5. Paula Kim, President/CEO Translating Research Across Communities (TRAC) and Research Advocate

The following model programs demonstrate the way that some advocates are involved in tissue research.

Model Programs

Arizona Myeloma Network Tissue Donor Awareness Project

The Arizona Myeloma Network's Tissue Donor Awareness Project was designed to increase patient awareness and understanding of the importance of providing tissue for cancer research and clinical studies. This project seeks to build a bridge of knowledge and communication among the cancer communities, including research investigators, doctors, and patients. To date, the program has conducted 3 focus group workshops in Arizona to promote awareness of the "Tissue Issue" or the need for tissue samples in cancer research.

Susan G. Komen for the Cure Tissue Bank at Indiana University Mel and Bren Simon Cancer Center

The Susan G. Komen for the Cure Tissue Bank at Indiana University is a national repository for tissue from women without breast cancer. This resource is available to scientists who are seeking to identify risk factors and biomarkers by comparing normal and cancerous tissue.

Initially called Mary Ellen's Tissue Bank, this organization spearheaded a program called *Friends for Life* at Indiana University Cancer Center. The ambitious project was designed to collect informed consent and blood samples from 1000 women in a single day. The women were also asked to complete a 5-10 minute questionnaire regarding personal demographics, current and past medications, menopausal status, breast cancer history, and other information. A total of 160 doctors, nurses, lab technicians, secretaries, nursing students, high school students, medical students, fellows and consumers volunteered to run the various workstations. On this single day – in less than 6 hours – the project successfully met its goal.

In 2007, the Susan G. Komen for the Cure organization earmarked \$1 million to expand Mary Ellen's Tissue Bank into a national resource, which continues as the Susan G. Komen for the Cure Tissue Bank.

Inflammatory Breast Cancer (IBC) Research Foundation BioBank

The IBC Research Foundation BioBank is a secure, privacy-protected collection of biospecimens from patients diagnosed with inflammatory breast cancer, as well as those not diagnosed with inflammatory breast cancer (controls). This biobank provides a resource for those studying inflammatory breast cancer, which has a low incidence that makes it difficult to obtain adequate tissue for study. The IBC Research Foundation Biobank focuses on giving patients control over what happens with their tissue and protecting patient rights.

Research Advocacy Network Tissue Awareness Program

Research Advocacy Network has developed several booklets related to tissue awareness entitled "Why is it important for me to consider donating my tissue for research?" and "The importance of tissue samples in research." The first booklet is designed for prospective tissue donors. The latter booklet provides background on the importance of tissue donation for members of Institutional Review Boards and Ethical Review Boards. These booklets are available at the Research Advocacy Network Website (<http://www.researchadvocacy.org/publications/posters.php>).

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GLOSSARY

Biomarkers: laboratory measurements that reflect the activity of a disease process. These often take the form of proteins or other biological substances that are used to identify cancerous cells; for instance, biomarkers may be proteins in the blood (serum biomarkers) or associated with tumor cells (often called tumor biomarkers)

Biopsy: the removal and examination, usually microscopic, of tissue from the living body

Biospecimen: a biological sample taken to show or to determine the character of the whole

Calibrate: to determine the accuracy of an instrument

Chromatin: the substance of chromosomes that is made up of DNA, protein, and chromosomal RNA

Chromosomes: structures in the nucleus of a cell that contains DNA, which contains genetic information

Clinical pathology: diagnosis and descriptions based on chemical composition of tissues/blood as determined by pathological tests

Clinical utility: the overall usefulness of a test in clinical practice, as determined by weighing its benefits and drawbacks information

Clinical validity: the ability of a test to provide clinically useful information

Correlative science: as used in this booklet, refers to the relationship between pathological findings (science) with clinical outcomes (long-term results)

Custodianship: guardianship; a person or organization in possession of a tissue specimen; custodians have responsibility as specified in the informed consent to fulfill the research participant's intentions

Differentiated: in the context of this booklet, refers to cells that show the characteristics normal for their type

DNA: deoxyribonucleic acid; the genetic material of all cellular organisms

Fixative: a chemical used to preserve tissue in a stable state and prevent deterioration

Genes: segments of DNA that contain the information required for synthesis of a product such as a protein

Genome: all of a living thing's genetic material

HER-2: human epidermal receptor growth factor-2; a protein involved in normal cell growth that is found in high levels on some breast cancer cells

Histology: the microscopic anatomy of tissue

Human Genome Project: an international scientific and research undertaking that had as one of its goals the sequencing of the entire human genome (goal was met in 2003)

Markers: see biomarkers

Molecule: a combination of atoms that forms a chemical substance

Outcome: long-term clinical results such as disease-free survival

Pathology: the branch of medicine that deals with the structural and functional changes in tissues and organs of the body that cause or are caused by disease

Philadelphia chromosome: an abnormality of chromosome 22 in which part of chromosome 9 is transferred to it. Bone marrow cells that contain the Philadelphia chromosome are often found in chronic myelogenous leukemia.

Prognosis: the likely outcome or course of a disease; the chance of recovery or recurrence

Reliability: the likelihood that a test will give the same result each time

RNA: ribonucleic acid; one of the two types of nucleic acids found in all cells. In the cell, RNA is made from DNA (the other type of nucleic acid), and proteins are made from RNA

Sample: a representative part taken to identify the whole

Sensitivity: the ability of a test to give a positive result when the thing we are looking for is actually present

Serum: the clear liquid part of the blood that remains after blood cells and clotting proteins have been removed

Specificity: the ability of a test to give a negative result when the thing we are looking for is not actually present

Specimen: a sample or part of a thing taken to show or to determine the character of the whole

Standardization: in this context, refers to the bringing of a test to compare or conform to an established measure

Surveillance: the ongoing collection of information about a disease, such as cancer, in a certain group of people. This may include information about whether cancer affects people of a certain gender, age, or ethnic group.

Tissue: a group or layer of cells that work together to perform a specific function

TNM: a system for describing the extent of cancer in a patient's body. T describes the size of the tumor and whether it has invaded nearby tissue, N describes any lymph nodes that are involved, and M describes metastasis (spread of cancer from one body part to another)

Tumor: an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancerous), or malignant (cancerous). Also called neoplasm

Undifferentiated: a term used to describe cells or tissues that do not have specialized ("mature") structures or functions. Undifferentiated cancer cells often grow and spread quickly

Validity: the accuracy of a test

Glossary Sources

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APPENDIX: ORGANIZATIONS IN WHICH ADVOCATES ARE INVOLVED

The following organizations are examples of ways that advocates are involved in research.

Institutional Review Boards

Institutional review boards (IRBs) are independent committees made up of individuals with diverse medical and non-medical backgrounds that review and approve all documents related to every study that involves human participants at a research institution. Every major institution that conducts research with human participants and has federal funding of their research must have an IRB. The primary purpose of the IRB review is to protect and assure the safety, rights, and welfare of study participants. An IRB approves a variety of different materials, including study protocols, informed consent forms, and participant recruitment materials. The IRB can approve or disapprove research or can require modifications that it feels are in the best interest of the participants. IRBs typically consist of researchers, physicians, students, community members (non-affiliated members, non-scientific members) who are not research experts, ethics experts, and/or lawyers. Because IRBs provide local protections, they are an ideal place for advocates.

Protocol Review Committees

Protocol review committees evaluate, approve or reject, monitor, and re-review human research protocols. A protocol is a description of the way a study is performed, including the number and characteristics of individuals to be enrolled, the procedures that participants undergo, and how the data are collected and analyzed. Protocol review committees may also examine whether the research study is designed to answer an important question, whether the study is adequate to answer the question, and whether the study can actually be completed as designed. Protocol review committees are distinguished from IRBs because they are focused on the research design, methods, and scientific merit, whereas IRBs are focused on the protection of participants. Protocol Review Committees have a similar member composition as IRBs; that is, they include research experts and may include advocates.

Data and Safety Monitoring Boards

Data and safety monitoring boards (DSMBs) oversee the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data. These boards monitor data that are generated to make sure that the treatment isn't unexpectedly harming subjects and to assess whether the treatment is so valuable that the trial should be stopped and everyone given the new treatment. DSMBs also close trials because of slow accrual. Data safety and monitoring boards are required by the National Institutes of Health (NIH) for all of the Phase III studies they support financially.

Study Sections (National Cancer Institute)

Study sections are part of all National Institutes of Health (NIH) divisions, including the National Cancer Institute. Study sections are groups of individuals organized around scientific areas, which review applications for federal research grants within that area. The money for these grants comes from our tax dollars. The study sections are made up of non-NIH scientific experts who are typically peers (i.e., they are researchers themselves) and, more recently, advocates and others such as lawyers. Study sections make recommendations as to the priority of the research, by way of a score, which is then taken into account by the National Cancer Institute in deciding which research to fund.

Patient Representative or Advocacy Committees in Cooperative Groups

These committees have been established by various oncology cooperative groups such as the Eastern Cooperative Oncology Group (ECOG) to incorporate the patient perspective into their organization and operation. Nearly all Phase III trials currently being designed in the Cooperative Groups incorporate a correlative science component in addition to the clinical component. The scientific component typically involves the study of participant tissue for clues about cancer – what causes it, which treatments might work, etc. Advocates are key to improving researchers' understanding of patient concerns about providing their tissue for cancer research.

Specialized Programs of Research Excellence (SPORE) at the National Cancer Institute

These programs were established in 1992 to promote interdisciplinary research and facilitate exchange between basic and clinical science. The goal of these programs is to incorporate novel ideas for reducing cancer incidence and mortality found in the laboratory into clinical research that will improve survival and quality of life for cancer patients.

Advocates can participate in SPORE's Patient Advocate Research Team (PART) Program. The PART Program helps SPOREs build effective collaborations with cancer patient advocates. Most SPORE patient advocates are willing to make a personal commitment to work directly with cancer researchers in a specific SPORE program.

Currently, patient advocates work with approximately 50 of the 58 SPORE programs throughout the U.S. While most SPORE programs include patient advocates at an advisory level, at least 25 programs involve patient advocates at an operational level. SPORE patient advocates can be involved in a wide range of activities, including:

- Input on strategic direction
- Grant reviews
- Tissue issues: consent forms, collection processes, usage, patient follow-up procedures
- Clinical trials
- Development: input on design, informed consents, IRB representation
- Accrual: letters on clinical trials, presentations to patient groups
- Adherence: support and guidance for patients, input for amendments
- Education: newsletters; forums and "training days" for patient advocate community; presentations in professional training courses (to scientific staff)

More information can be obtained from the homepage (www.nci.nih.gov) or at the following link: <http://spores.nci.nih.gov/>.

Consumer Advocates in Research and Related Activities (CARRA)

The National Cancer Institute (NCI) of the National Institutes of Health has established a novel program designed to integrate the views of the cancer community in directing Institute activities and research. CARRA includes roughly 200 cancer survivors and consumer advocates from across the country. The members of CARRA are diverse in terms of the types of cancer with which they are familiar, as well as their ages, and ethnic origins. CARRA

members not only serve as an integral part of NCI activities, but also as liaisons linking back to the cancer community networks. CARRA members serve 3-year terms and are called upon as needed for input into particular activities, including peer review of grant applications and evaluation of information geared toward the cancer community. CARRA was developed to make the input of advocates more systematic and routine and to facilitate two-way communication between the Institute and the community.

More information can be obtained from the homepage (<http://carra.cancer.gov>).

Patient Representative Program at the Food and Drug Administration

In this capacity, advocates provide the patient and family perspective on issues, problems, and questions related to the viewpoint of patients and family members living with a specific, serious or life-threatening disease. Advocates may be voting or non-voting members of the advisory committee. More information can be obtained from the FDA's homepage (www.fda.gov) or at the following link: <http://www.fda.gov/oashi/patrep/patientrep.html>.

National Biospecimen Network

The National Biospecimen Network also poses opportunities for advocate participation. Information about advocate participation can be obtained at the National Biospecimen Network website by clicking on Contacts (<http://prostatenbnpilot.nci.nih.gov/contact.asp>).

Ethnically- or Culturally-Based Initiatives

A number of ethnically- or culturally-based initiatives have been undertaken to provide support, information, and programs for specific groups of people who are united by a common heritage. Such initiatives are particularly important in genomics, as certain genetic variations may be more common in some subgroups of individuals than others. Following is a non-comprehensive list of some ethnically- or culturally-based initiatives.

Genetic Education for Native Americans (GENA)

Genetic Education for Native Americans is a project designed to provide culturally competent education about genetics and genetic research to Native American college and university students. The secondary goal is to increase the number of Native American people who have access to scientific mentoring experiences in genetic counseling, education, research, and other opportunities or careers. The GENA project is comparing two variations of a newly designed culturally relevant genetic education program and provides mentoring opportunities to Native American students who are interested in genetic education, research and medicine. More information is available at the following website: <http://members.aol.com/natamcan/gena.htm>.

Native American Cancer Survivors' Support Network

Native American Cancer Survivors' Support Network offers social and emotional support and culturally-specific educational materials to cancer patients and survivors. It conducts one-on-one interviews with survivors to learn more about how they are dealing with their cancer and how their care can be

improved. It also connects members with other Native American survivors who have had similar experiences. An important activity is the support of a confidential database to monitor members and track the types of cancer and cancer care. More information can be found at the homepage www.natamcancer.org or at the following link: <http://natamcancer.org/community.html>.

Redes En Acción: The National Hispanic/Latino Cancer Network

Redes En Acción is an initiative designed to combat cancer among Latinos. This National Cancer Institute-funded initiative focuses on cancer prevention and control by building a nationwide network of community-based organizations, research institutions, government health agencies, and the public. Core activities include promoting training and research opportunities for Latino students and researchers, generating research projects on key Latino cancer issues, and supporting cancer awareness activities within the Latino community. More information is available at the following website: <http://www.redesenaccion.org/>.

Sisters Network, Inc.

Sisters Network, Inc. is a national African-American breast cancer survivorship organization with 39 affiliate chapters around the nation. It provides support, breast education programs, resources, information, and research through its affiliated chapters. In 1999, Sisters hosted the nation's first national African-American Breast Cancer conference to specifically address the impact of breast cancer among black women, which is now in its sixth year. Community outreach programs include "The Gift for Life Block Walk™" The Pink Ribbon Awareness Campaign, STOP THE SILENCE: Changing the Face of Early Breast Health Intervention, and The S.P.I.R.I.T. program, a national partnership with the UT M. D. Anderson Cancer Center. More information is available at the following website: www.sistersnetworkinc.org.

Intercultural Cancer Council

The Intercultural Cancer Council (ICC) promotes policies, programs, partnerships, and research to eliminate the unequal burden of cancer among racial and ethnic minorities and medically underserved populations in the United States and its associated territories. The ICC works to facilitate the access of minorities and medically underserved populations to the healthcare system. It also strives to include survivors, minorities and culturally diverse individuals in the development of health policies and programs intended for their communities. More information is available at the following website: <http://iccnetwork.org/>.

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Research Advocacy Network

Advancing Patient-Focused Research

www.researchadvocacy.org