The Importance of Tissue Samples in Research

Research Advocacy Network

Advancing Patient-Focused Research

This booklet was developed by the Research Advocacy Network. The mission of the Research Advocacy Network is to advance patient-focused research by fostering interactions among advocates, researchers and organizations.

The purpose of this booklet is to provide some background information for Institutional or Ethical Review Boards (IRBs or ERBs) on studies that involve collection of tissue for research. We hope the booklet will support the IRB and ERB community in their work of protecting patients participating in the research process as well as highlighting the importance of research on tissue from patients.

The focus of the booklet is on the views and needs of cancer patients who participate in research by donating their tissue. Included is information on studies that have looked at the willingness of patients to donate their tissue, the new scientific advances made possible by tissue research and the importance of informed consent for tissue research.

This booklet is organized around the answers to the following questions:

- Why cancer patients consider donating tissue for research?
- What are the risks of donating tissue?
- How is privacy and confidentiality protected?
- What should informed consent documents contain to explain tissue research to patients?
- What other patient concerns could be addressed in an informed consent document?

For the purposes of this booklet, tissue is defined as: everything from subcellular structures like DNA, to cells, tissue (bone, muscle, connective tissue and skin), organs (e.g. liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, placenta). In addition, each specimen of human tissue may be stored in multiple forms, such as slides, formalin fixed – paraffin wax embedded blocks, frozen, tissue culture, or extracted DNA.
Tissue provides information that helps clinicians diagnose cancer and make appropriate treatment decisions. The tissue collected for staging and diagnosis may include a small portion of a tumor. Blood, urine, bone marrow, lymph nodes, fluid or sputum may also be used for diagnosis. All of these things are referred to as tissue in this booklet.

At least three kinds of tissue are used in research.

1. *Residual or extra tissue taken for the patient's diagnosis and treatment.*
2. *Tissue taken specifically for research purposes, e.g., blood.*
3. *Excess normal tissue.*

Research on tissue may provide information that will help prevent, diagnose and treat cancer patients in the future. The more annotated a tissue sample, (the more patient information accompanying the sample), the more valuable it is to the research community. This means that in many cases cancer patients are being asked to donate both their tissue sample and the medical information attached to that sample.

Why cancer patients consider donating their tissue for research

There are two reasons cancer patients support tissue research:

1. *Patients hope tissue research may help them and/or their families deal with cancer.*
2. *Research on tissue may provide information that will help prevent, diagnose and treat cancer patients in the future.*

Research on tissue may provide information that will help prevent, diagnose and treat cancer patients in the future. For example, finding which patients respond better to or have fewer side effects from a particular drug. The patient may not directly benefit from donating tissue but the research on their tissue may benefit patients in the future. (See Scientific discoveries through tissue)

Research Supports Participants' Willingness to Donate Their Tissue

The National Cancer Institute (NCI) in the United States of America (USA), conducted focus groups with individual patients and patient advocate organizations surveying them about their willingness to consider donating their tissue and data for research. An overwhelming number, 90% +, of patients said they would be willing to donate their tissue for research purposes. They did request that 1) their tissue be used for "good" research and 2) the research would advance the treatment for future patients.

The report from the NCI patient focus groups stated, "All the participants were supportive of providing tissue for research. They felt it was a worthy contribution that could lead to cures for diseases or prolong people's lives."[1]

The Eastern Cooperative Oncology Group (ECOG) collected data about patient response to donating tissue for cancer research in trials they conducted between 2/10/98 and 10/31/00. They used two different consent forms. ECOG registered 5,411 patients on 40 trials using the first form asking explicitly if specimens could be banked for future research. Using the one question form, 89.4% of patients responded positively. The second form expanded the number of questions to be answered by the patients. Patients responded positively 93.7% using the 3-question form. They concluded that, "…additional subject protections have not impacted on the availability of ECOG samples for future correlative research."[2]

"One report from the MONICA project in Sweden found that 11 years after samples had been collected, 93% of eligible participants gave their consent for the stored samples to be used for academic research…."[3]

In the published paper, "Why surgical patients do not donate tissue for commercial research: review of records,"[4] of the 3140 preoperative patients interviewed, only 38 (1.2%) refused to allow their tissue to be used for commercial research. In the interviews conducted by a trained research nurse they found, "Patients awaiting surgery are often pleased and even grateful to have been given an opportunity to play a part in research, which could in the future possibly benefit other people, including their family."

Tissue is critical to the accurate diagnosis and staging of cancer. It helps the patient and their doctor make appropriate treatment decisions, giving the patient the best chance of disease-free survival. The study and analysis of tissue by researchers is necessary for cancer research. Studying tissue could ultimately lead to scientific discoveries for the prevention, diagnosis and treatment of cancer patients in the future.

What are the risks to patients when they donate tissue?

Physical Risks
Depending on the type of tissue being taken and the way it is taken, the patient may experience:

- Pain at the biopsy site or needle puncture site
- Bruising/swelling at the place where the tissue is taken
- Risk for infection

For other types of research a biopsy or blood sample will not need to be taken. Instead, a small portion of the tissue previously taken to diagnose the presence of cancer will be obtained. The tissue taken to diagnose cancer is saved by being stored in paraffin wax and called a tissue block. The tissue block is stored in the pathology department of the hospital where the person was diagnosed. Only a small piece of the tissue block is needed for most research projects.

All cancer is genetic. This does not mean that all cancer is inherited but rather all cancer is caused by changes in our genes. Most of these changes or mutations can occur in any type of cell (e.g., lung, colon, liver) at any point in our lifetimes. The changes can give rise to cancer in those particular cells (e.g., lung cancer, colon cancer, liver cancer).

Whether or not a mutation can be passed on to the next generation depends on the type of cell in which it occurs. Mutations can occur in our germ cells or

somatic cells. Germ cells are the reproductive cells in our bodies, either egg or sperm cells. In contrast, somatic cells are all of the non-reproductive cells in our bodies such as liver cells, skin cells, and muscle cells.

Because only our reproductive cells form an embryo, only mutations in these cells can be passed on to the next generation. Mutations that can be passed on to the next generation are called hereditary or germline mutations. There may be emotional risks and benefits in knowing that you have a genetic mutation and emotional benefits in knowing you do not have a genetic mutation that could indicate cancer in the future. The history of BRCA1 and BRCA2 is a good case study on germline mutations and the emotional impact of knowing you carry a gene for cancer.[5, 6]

In contrast, mutations in somatic cells such as our liver cells, blood cells, stomach cells, and all other non-reproductive cells cannot be transmitted to the next generation. These are called somatic mutations.

Non-physical Risks

Most tissue research does not provide the type of individual medical information that would affect the family, insurance or employment. However there is a remote possibility of the following types of risk to the research participant.

Social Risks

The social risks of donating tissue include:

- Loss of privacy – How researchers identify the medical information may allow others to know that information
- Breach of confidentiality – If researchers disclose medical information in an unauthorized way, others may have access to information and use it in a way that is harmful to the individual.

Some types of tissue research raise concerns over:

- Insurance discrimination – An insurer refuses to provide the patient with insurance coverage because the study of their tissue identified a gene making the individual more likely to get a disease or condition in the future, thus making the individual a poor insurance risk.

- Employment discrimination – An employer refuses to hire or promote the patient because of information found through the research of the individual's tissue.

- Family conflicts –Some family members may not want certain medical information from the patient's tissue sample disclosed, while other family members may want medical information disclosed to them.

What protections exist to minimize risks and ensure the privacy and confidentiality of medical information?

There are laws and regulations that govern:

- how tissue is collected and stored,
- the type of information researchers must provide to participants before they agree to participate or donate tissue,
- how medical information from tissue may be provided to others and under what circumstances.

Protections for collection of tissue

Ethically, all research of any kind should be reviewed by an IRB or ERB. These review boards exist in every institution to ensure that the rules and regulations pertaining to research with people are strictly followed. All drug research requires some level of IRB or ERB approval. The IRBs and ERBs analyze whether the anticipated benefits of research are worth the risks. They protect tissue donors by requiring voluntary participation and full disclosure of research procedures, risks, rights, and responsibilities.

Protections for tissue storage

Protecting tissue storage and handling assures the patient that their tissue will not be lost due to poor practices. A number of professional organizations around the world have or are developing standards and "best practices" for tissue repositories or banks. For example, the International Society for Biological and Environmental Repositories (ISBER), the National Biospecimen Network, the College of American Pathologists and the UK Biobank. These standards and "best practices" detail policies and procedures that emphasize quality assurance and cover collection, freezing/fixing, storing and shipping of specimens.

Certificates of Confidentiality (USA only)

Certificates of Confidentiality are issued by the National Institutes of Health in the USA and are a way of protecting the privacy of research participants. Certificates of Confidentiality are issued to institutions conducting research and protect investigators and institutions from compelled disclosure of participants' identifying information to any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals. "Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects, such as damage to their financial standing, employability, insurability, or reputation." Researchers may voluntarily disclose information but if they plan to do so, the consent form should inform the participant.[7]

Protections required of sponsor's

Sponsors or investigators requesting approval to collect, store and perform research on biological specimens, need to provide IRBs/ERBs with adequate information to make a proper assessment prior to granting approval of the research study. Such

information may include the following:

1. *Nature of the research.*
2. *How tissues will be obtained, processed and distributed.*
3. *Whether any identifying information such as name or address will be collected.*
4. *How tissues will be labeled to protect patient privacy. For example, using a unique identifier or code number in place of the patients' name.*
5. *How identifiers will be linked to specimens (e.g. de-identification, anonymous, linkable, etc).*
6. *How clinical data will be associated with the specimen and how that clinical data will be collected.*
7. *Informed consent document that stipulates exactly how the specimens will be used, how the remaining material, if any, will be disposed of.*
8. *Information on whether or not patients will receive the results of the research on their sample.*
9. *How participants' rights will be protected with any future use of the specimens not previously approved by an IRB. For example, a policy that assures all "future proposals for subsequent use of specimens will require IRB/ERB approval prior to release of any specimen or linking to personal health information. This could be performed by a regulatory compliant IRB or ERB designated to oversee/approve the activities of the researcher.*

Protections for privacy of health care information

Every country has laws and regulations that protect the privacy of patients' identifiable health care information such as name, age, address etc. For example, The Health Insurance Portability and Accountability Act (HIPAA) in the USA, the European Union Data Protection Directive (95/46/ED) and Japan's Personal Information Protection Act. These laws provide safeguards against the inappropriate dissemination of medical information.

For both regulatory and ethical reasons, tissue samples and medical information about tissue donors are ordinarily provided with a code number rather than with information that can readily be used to identify the donor (e.g. name and address.) This code number is a way of 'de-identifying' data or samples and enables scientists to conduct research without knowing personal details of the tissue donor.

Informed Consent

Most countries have specific laws and regulations that require researchers to fully inform patients of how their tissue will be taken and how it will be used in research. The researcher conducting the study is responsible for providing adequate informa-

tion to fully inform the participant of the risks and benefits of participation/donation. Patients must give consent for their samples to be used in research before their tissue samples are collected.

The informed consent regulations require researchers to explain the following in compliance with local laws and regulations:

- how the tissue will be collected and used in research
- how medical information will be stored
- when and how the tissue will be obtained
- risks of obtaining the tissue.
- how patient privacy and confidentiality will be protected

Patients may restrict the use of tissue to particular types of research, e.g., research specified in the consent, cancer research, other health related research.
If the tissue is waste tissue and is used without traceable identifiers, the research is eligible for a waiver of consent and may qualify for exempt status.
If samples of normal tissue (tissue not collected for diagnosis and treatment) are required by the research it must be made clear to the participant and should be restated in the consent form.
Tissue for research should only be collected after a patient signs the informed consent document.

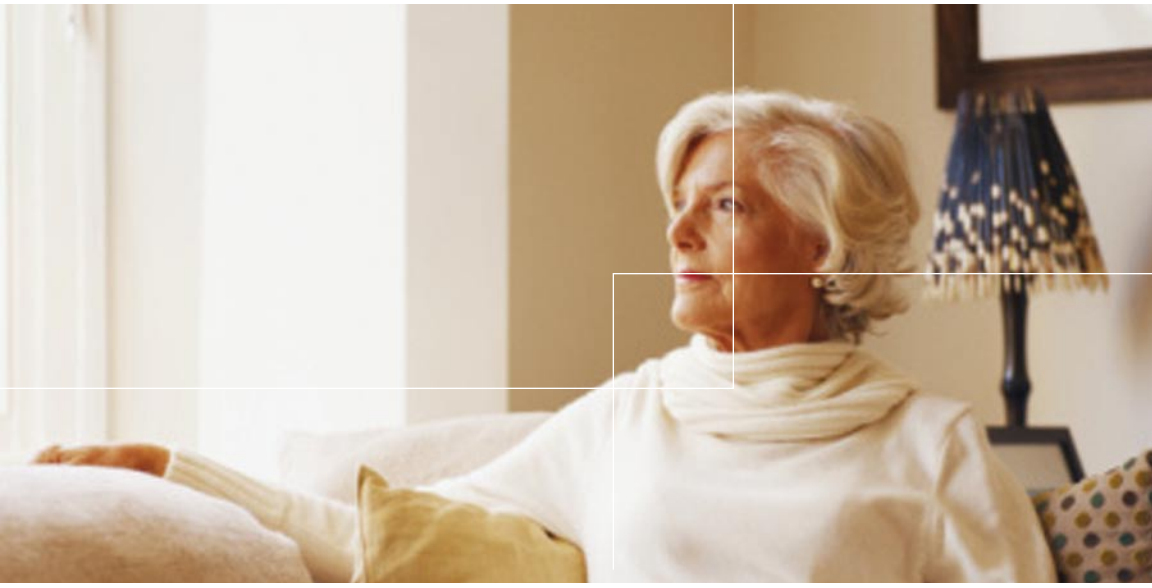
Other patient concerns that could be addressed in an informed consent document

- Access to the tissue sample – Patients may want access to the tissue after it has been collected. For example, in cases where markers associated with clinical benefit or potential cancer risk that would be important for close monitoring family members are identified. The informed consent document should tell a patient if all of their sample will be used or destroyed through the research process.

- Religious or philosophical concerns – patients may be religiously or philosophically opposed to the research conducted on their tissue sample.

- Ownership - One question that arises when people donate their tissue is the question of ownership. Who owns the product or intellectual property that could come from using or analyzing tissue and who will profit from that ownership? Donation of tissue is much like any other donation, e.g., giving a cash donation to a charity, it is a transfer to another person or entity, usually with no strings attached. Something must be done to, or with, the tissue that adds commercial value and it is this value-added data that is considered intellectual property and protected by law. It is the analysis of many tissue samples that leads to most discoveries. Patients should be informed that they will not profit from any commercial product that may come from the study of their tissue and it should be restated in the consent form.

- Results – The informed consent document should inform the participant whether they will be told the results of research done on their tissue sample. The value of research using tissue comes from combining all the individual results and identifying patterns, e.g., most people with gene Q have a higher survival rate; only a very small percentage of people with gene K have cancer that spreads. It is the overall finding or patterns that are then reported by being published in scientific journals or made available on company websites. If the participant will be informed of these results, the informed consent document should tell the individual when, how and by whom they will be given this information.



Scientific discoveries through tissue:

Learning how cancer cells work.
The study of tissue allows us to learn more about how cancer cells work. The knowledge of how cells work, tied to the outcomes of treatment for people who donate their tissue, will provide valuable information for future treatment. An excellent example of this is the role of estrogen receptors in breast cancer cells. Through the analysis of tissue from breast cancer patients, scientists were able to identify that some breast cancer tumors had multiple estrogen receptors (structure on the surface of a cell (or inside a cell) that selectively receives and binds a specific substance) in their cells. This confirmed the theory that the body's own estrogen was "fueling" tumor growth. In estrogen receptor positive (ER+) tumors, blocking the estrogen receptor with drugs such as tamoxifen (Nolvadex) or decreasing the amount of hormones in the body with drugs like anastrozole (Arimidex) could reduce the recurrence of cancer. It was only through the generosity of women with breast cancer who donated their tissue that researchers were able to improve treatment.

Finding targets for new drugs.

Gefitinib (Iressa) and Erlotinib (Tarceva):
Gefitinib and erlotinib are so-called targeted therapies, in that they stop the growth of certain cancers by zeroing in on molecules that send signals to cancer cells that are critical to their survival. They target a gene in tumors that produces an epidermal growth factor receptor (EGFR). EGFR is found on the surface of some lung, pancreatic and other cancer cells, that helps tumors grow and spread. Gefitinib and erlotinib block this receptor.

Both drugs have been tested in US patients with non-small cell lung cancer (NSCLC); however the two drugs are effective in only 10% of patients. To understand why only a small number of patients responded, researchers analyzed tumor samples from NSCLC patients. Scientists found that the two drugs worked specifically in patients whose cancers contain mutations in the epidermal growth factor receptor (EGFR) gene. Because of the difference in how patients responded to these drugs, it was hoped that a test could be done to determine which patients had the mutation in the EGFR gene. In a larger study done in Canada tissue was analyzed for mutations in the EGFR gene and then compared to the response of NSCLC patient to erlotinib. Researchers found that the presence of the mutation did not predict responsiveness to erlotinib.

It is too early to tell if this mutation in the EGFR gene will be able to predict which patients will respond to these new drugs. The tissue donated from patients and studied by researchers will ultimately give us an answer.

Imatinib (Gleevec):
Imatinib represents a new approach to cancer treatment, one that targets the unique genetic defects present in tumors. It was approved in 2001 for the treatment of some types of leukemia. Imatinib also appears to work in a rare type of cancer called gastrointestinal stromal tumor (GIST).

The majority of GISTs have a mutation in a protein known as KIT, which is responsible for the processes that regulate growth and multiplication of cells.

In the treatment of GIST imatinib is thought to work by blocking the KIT pathway, which then stops the cancer from growing. Because of how different patients respond to imatinib, researchers wanted to know if understanding KIT mutations would help provide a link between responders and non-responders after treatment. Scientists obtained tumor samples from 324 patients diagnosed with GIST. Of the 324 patients, 280 were found to have KIT mutations. Researchers concluded that certain KIT mutations are associated with significantly higher response rates and longer time to cancer progression intervals among patients treated with imatinib. Genetic mutations in KIT appear to predict which tumors will respond to the drug. The study indicates the importance of profiling patients in order to individualize

therapy, which ultimately may provide a better outcome for the patient. This is one more example of a study that was done analyzing tissue donated by patients.

Identifying causes of cancer

The information gained from the analysis of tissue samples may help identify the causes of cancer. Linking genetic factors and environmental exposures, such as, diet, culture, toxins, microorganisms and parasites, and life style choices may tell us more about what causes or contributes to the development of cancer. Information from tissue may help us understand how personal, familial and ethnic factors affect our susceptibility to diseases like cancer.

References

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Additional Information

For more information, please see the following:

- Health Insurance Portability and Accountability Act (HIPAA) http://www.hipaa.com/
- Cato Institute, Privacy and Human Rights: Comparing the United States to Europe http://www.cato.org/pubs/wtpapers/991201paper.html
- European Union Data Protection Directive (95/46/ED) http://www.cato.org/pubs/wtpapers/991201paper.html
- Japan Personal Information Protection Act (2003) www.privacyexchange.org/japan/JapanPIPA2003v3_1.pdf
- NIH Office of Human Research Protections http://www.hhs.gov/ohrp/
- Belmont Report, http://www.med.umich.edu/irbmed/ethics/belmont/ BELMONTR.HTM
- Moore Case http://www.forhealthfreedom.org/Publications/Informed/WhoOwns.htmlhttp://www.forhealth-freedom.org/Publications/Informed/WhoOwns.html, http://www.bioethics.uu.se/chapters/JDRendtorff.pdf
- National Bioethics Advisory Commission Report (1999) Research Involving Human Biological Materials: Ethical Issue and Policy Guidance, http://www.nlm.nih.gov/pubs/cbm/hum_exp.html
- National Dialogue on Cancer National Biospecimen Network Blueprint, http://prostatenbnpilot.nci.nih.gov/blue_full6.asp
- International Society for Biological and Environmental Repositories, http://www.isber.org.
- UK Biobank http://www.ukbiobank.ac.uk/
- Lymphomation.org, The National Biospecimen Network http://www.lymphomation.org/NBN.htm
- Certificates of confidentiality, http://grants.nih.gov/grants/policy/coc/background.htm