

Meeting Research Needs with Postmortem Biospecimen Donation: Summary of Recommendations for Postmortem Recovery of Normal Human Biospecimens for Research

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Normal human tissues, bodily fluids, and other biospecimens of known quality are essential for research to understand the development of cancer and other diseases and to develop new diagnostics and therapies. However, obtaining normal biospecimens appropriate for contemporary large-scale molecular and genomic research is one of the most challenging biospecimen acquisition problems for scientists and biospecimen resources that support research. Recognizing this challenge, the U.S. National Cancer Institute recently convened a series of workshops and meetings focused on the acquisition of normal tissues for research and produced an extensive document, *Recommendations for Postmortem Recovery of Normal Human Biospecimens for Research*. This article summarizes these recommendations, addressing key ethical, operational, and scientific elements for collecting normal reference biospecimens from postmortem donors in the U.S. Awareness of these recommendations can foster more effective collaborations and mitigate potential logistical challenges, while promoting postmortem biospecimen donation options for families and increasing the availability of high quality normal biospecimens for research. The recommendations have been put into practice in the collection of normal human biospecimens for the NIH Genotype-Tissue Expression Program (GTEx), a pilot study of human gene expression and regulation in multiple tissues which will provide valuable insights into the mechanisms of gene regulation and, in the future, its disease-related perturbations (<http://commonfund.nih.gov/GTEx/>).

Introduction

WELL-ANNOTATED NORMAL HUMAN tissues, bodily fluids, and other biospecimens of known quality are essential for research to understand the development of cancer and other diseases. Normal human biospecimens are an essential comparator tissue used for a variety of disease research applications, including the development of new diagnostics and therapies. However, obtaining normal biospecimens appropriate for contemporary large-scale molecular and genomic research is one of the most challenging biospecimen acquisition problems for scientists and biospecimen resources supporting research. The quality of normal biospecimens collected from living or deceased donors can be compromised by the interventions of standard medical treatments, end-of-life support, and even the process of research biospecimen procurement itself. Such preanalytical factors can intrude into the normal physio-

logical milieu of biospecimens and alter normal biology, and thus alter the outcome of molecular studies based on these biospecimens.

Since the 2003 publication of the *National Biospecimen Network Blueprint*,¹ the importance of high-quality specimens and standardized biobanking practices has been increasingly recognized by scientific and governmental institutions²⁻⁵ and the popular press.⁶ The National Cancer Institute (NCI) has sponsored several initiatives to develop and disseminate best practices and recommendations aimed at improving the acquisition and quality of human biospecimens for research, including the *NCI Best Practices for Biospecimen Resources* (2007, updated in 2011).⁷ During 2010–2011, a series of workshops and meetings of invited experts were convened as part of a planning process for a national center for biospecimen science and standards, the cancer Human Biobank (caHUB). One of the planning groups focused on the acquisition of normal tissues for research and produced an extensive document, *Recommendations for*

Biorepositories and Biospecimen Research Branch, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. Individual members listed in Appendix 1. The contents of this publication do not necessarily reflect the views or policies of the U.S. Department of Health and Human Services or the National Institutes of Health.

Postmortem Recovery of Normal Human Biospecimens for Research (<http://biospecimens.cancer.gov/resources/oe/pr.asp>). The recommendations have been put into practice in the collection of normal human biospecimens for the NIH Genotype-Tissue Expression Program (GTEx), a pilot study of human gene expression and regulation in multiple tissues which will provide valuable insights into the mechanisms of gene regulation and, in the future, its disease-related perturbations (<http://commonfund.nih.gov/GTEx/>). This article summarizes these recommendations, addressing key elements for collecting normal reference biospecimens from postmortem donors, with the overarching goal of increasing the availability of high quality normal biospecimens for research.

Summary of Recommendations

Defining "Normal" for research donors and biospecimens

"Normal" tissues for research can include multiple assorted reference tissues from the human body that are used to study human health and disease. "Normal" tissues for research commonly refer to tissue types corresponding to organs frequently afflicted by cancer or other diseases and that are recovered from individuals free of the given disease. Moreover, it should be noted that a broad label such as "normal" may be less useful than a relative definition in the context of specific research interests. Normal reference tissues may therefore be broadly characterized according to three general levels: (a) Molecular Profile. A tissue sample may be labeled as "normal" based on having no detectable evidence of disease in the range of sensitivity of a specific diagnostic test that has been conducted on it; (b) Morphology and Histology. A tissue sample devoid of macroscopic and microscopic (pathological) evidence of disease may be labeled as "normal."; (c) Donor Medical History. A tissue sample may be labeled as "normal" if it comes from a donor with no history of chronic or acute disease.

Types of postmortem biospecimen recovery partners

In the U.S., postmortem biospecimen recovery for research typically involves a partnership with a research biospecimen recovery program, most commonly a rapid autopsy (RA) program, organ procurement organization (OPO), or a tissue recovery organization (TRO), but may also include willed-body donation programs, medical examiners, funeral homes, and biospecimen collection networks.

Rapid autopsy programs. A rapid (or "warm") autopsy is performed soon after death for diagnostic purposes and with concomitant collection of biospecimens for research. RA programs are generally organized within academic medical centers and recover specialized biospecimens under specific inclusion criteria for research programs that are difficult or impossible to acquire by other means. The RA model has expanded in recent years to include brain tissue recovery, metastatic prostate cancer, metastatic pancreatic cancer, idiopathic pulmonary fibrosis, fibromyalgia, and multiple sclerosis.⁸⁻¹¹ Established programs include those sponsored by the NCI Specialized Programs of Research Excellence, the National Institute of Mental Health, and the National Institute of Child Health and Human Development, some of which have operated for more than 25 years.¹² Successful RA programs have a dedicated multidisciplinary team that in-

cludes attending physicians and residents, technicians, data managers, study nurses, and research coordinators. RA programs typically obtain consent for tissue donation from living donors if they are capable, or from next of kin.

Organ Procurement Organizations. The national network of Organ Procurement Organizations includes 58 OPOs that are federally designated by Centers for Medicare and Medicaid Services (CMS) to provide services for a specified donation service area. OPOs typically recover solid organs such as the heart, lung, liver, and kidneys, among others, for transplantation into individuals suffering from end-stage organ failure who require an organ transplant to survive. A large percentage of federally designated OPOs also recover tissues such as bone, soft tissue, cardiovascular tissue, and skin for transplantation, and work with partner tissue banks to process and distribute the recovered tissue. All OPOs must conform to Organ Procurement and Transplant Network (OPTN) rules and regulations and meet all CMS regulations and performance standards.^{13,14,15} All OPOs are also members of the Association of Organ Procurement Organizations (AOPO), which offers a voluntary accreditation program. Generally, OPOs are open to seeking ways to acquire and provide research biospecimens, and CMS regulations that promote research biospecimen acquisition offer incentives to participate. If an OPO recovers tissue for transplantation they must comply with the same requirements outlined below for Tissue Recovery Organizations.

Tissue Recovery Organizations. There are approximately 80 Tissue Recovery Organizations (TROs) throughout the country that primarily collect tissues for transplantation (e.g., bone, soft tissue, cardiovascular tissue, and skin); approximately 90 additional organizations exclusively recover ocular tissue. Federal law requires all hospitals to have an agreement with a tissue bank and an eye bank to provide for the recovery of transplantable tissues in the hospital. TROs must comply with FDA Current Good Tissue Practice (GTPs)¹⁶ and may seek voluntary accreditation from the American Association of Tissue Banks.¹⁷ TRO staff screen donors for relevant medical history and lifestyle risks, perform aseptic recovery procedures, excise tissue, and package recovered tissue appropriately for delivery. In addition to transplantable tissues, some TROs recover tissue specimens to fulfill specific requests from researchers; also, tissues originally collected for transplantation purposes may be released for research use (provided the appropriate donor or next of kin consent is in place) should the donor or tissues fail to meet transplant criteria for reasons such as donor serologic screening results or tissue bacterial culture results, or if the specific tissue types or sizes are determined to be surplus material that is unlikely to be transplanted. Recovery team personnel may include surgical technicians, paramedics, physician's assistants, emergency medical technicians, nurses, or other allied health professionals who have met the requirements and been awarded the designation of Certified Tissue Banking Specialists (CTBS) by the American Association of Tissue Banks.

Establishing research donor selection criteria

Organ recovery criteria for transplantation are rigorous but may vary depending on the transplant program, transplant surgeon, potential recipient, and the potential recipient's clinical condition at the time of transplant. Exclusion criteria for organ donors typically include conditions such as human immunodeficiency virus (HIV) and certain other transmissible

diseases. To assess donor suitability for a given research project, inclusion and exclusion criteria should be established on a per-project basis. Developing broad criteria will increase the number and diversity of potential research biospecimen donors. For normal postmortem biospecimen recovery, specifying general criteria and exclusions for certain medical conditions enables donor prescreening, although the approach may require donors who lack the required medical information to be excluded from consideration.

The maximum acceptable postmortem interval (PMI)—time from donor death to biospecimen recovery—should be clearly defined for each research biospecimen collection project. Typically, projects with a low-PMI criterion will collect and preserve biospecimens within 1–6 hours from death. The maximum PMI for most research tissue collection projects is typically 24 hours. With respect to research biospecimen recovery, every attempt should be made to recover biospecimens as quickly as possible following death of the donor, as time to preservation can be a major factor in biospecimen quality. Generally, PMI is inversely related to the integrity of RNA and other macromolecules—longer PMI correlates with poorer RNA quality. However, the effects of PMI on RNA quality vary significantly among organs and tissues and in some instances may be less important than other factors such as donor agonal state. Factors affecting molecular quality are discussed in more detail below (Postmortem Biospecimen Quality Control).

Identifying and screening postmortem donors

By law, all deaths in U.S. hospitals must be reported to the local OPO. On notification of the death, the OPO begins evaluating the patient as a potential donor for organ and tissue transplant. Some organizations will also assess the capacity of a deceased patient to donate for research, education, or therapy. OPOs and TROs prepare and utilize a donor risk assessment, which is an extensive questionnaire to evaluate potential donors for disease and to assess the donor's general health. The history generally includes questions regarding medical conditions, prescription drug use, alcohol and recreational drug abuse, smoking history, travel, and lifestyle. Generally, the donor criteria used by OPOs for whole-organ acceptance are stricter than those necessary for research tissues.

OPOs and TROs typically have call centers with trained staff to screen and discuss donation options with families. Donor screeners at the call center may be the first to rule out potential donors based on specified exclusion criteria. For patients who die in a hospital setting from a neurological insult or injury and are eligible for organ donation, the OPO first will approach the next of kin to request that he/she authorize an anatomical gift from the decedent. If the patient has previously indicated their desire to donate and is registered as such in the state's donor registry, the family is informed and asked to assist in facilitating the descendant's wishes. When patients expire in the hospital from respiratory or circulatory arrest and are not suitable for organ donation, an OPO or TRO will usually first approach the next of kin via telephone to request an anatomical gift. In many instances however, donors providing transplantable organs and tissues can also donate research tissues.

Coordinating the workflow of the recovery team

Transplantable organs are recovered immediately after death and other tissues for transplant are typically recovered

within 24 hours after death. If the body has not been refrigerated, transplant tissue recovery is typically completed within 15 hours after death. For transplant tissues, the screening and authorization process usually takes 2–6 hours, including contacting the next of kin and obtaining authorization and the donor risk assessment. Mobilizing a postmortem recovery team and (if required) transporting the donor may require an additional 1–2 hours. A given tissue recovery protocol may require an additional 1–6 hours to execute fully, thus creating an overall window of 4 to 14 hours from the time of donor death to completion of research recovery. This will vary depending on the location of the patient and the distance from the recovery team location.

Within the research recovery setting, a team of individuals usually prepare the donor and identify and excise organs and tissues for finer dissection. These excised organs and large samples can be transferred to members of a second team typically working on a back table or side table within the recovery suite, operating room, or morgue. The second team uses fine dissection methods to subdivide larger samples, according to standard histopathology tissue handling principles. This team is also generally responsible for packaging biospecimens into containers, tracking the containers' identifiers, and preserving the samples (usually in liquid nitrogen, dry ice, and/or formalin).

Maximizing the yield and quality of biospecimens recovered while maintaining appropriate respect for the donor and the donor's family should be the primary objectives of postmortem biospecimen recovery for research. These goals can be attained by collecting a large number of samples from one donor as part of a single research protocol or combining multiple compatible research collection protocols as appropriate. To facilitate the recovery of multiple biospecimens from a single donor, the panel of target biospecimens should be defined and prioritized for collection based on the requirements of the research project and organized according to anatomic region. Biospecimens may be collected sequentially so that those with the most labile macromolecules are obtained first and those most stable are collected last.

Once recovered, biospecimens may be transported directly to researchers for analysis or alternatively to biorepositories for quality control, redistribution, and/or short- or long-term storage. Best Practices for biorepositories are defined elsewhere, including the *NCI Best Practices for Biospecimen Resources* (2007, 2011).⁷

Postmortem biospecimen quality control

Comprehensive collection and management of donor-related biospecimen information supports biospecimen quality and promotes due diligence in donor screening and recruitment. The following data types are recommended when collecting postmortem biospecimens for research:

- Donor demographics
- Behavioral history (Risk assessment)
- Serology and infectious disease status
- Medical history
- Laboratory and pathology data
- Antemortem medical conditions
- Postmortem donor management information
- Biospecimen collection, processing, and storage information

Multiple molecular assays may be performed to assess biospecimen quality. These include assays on biospecimen-derived analytes such as DNA, RNA, and proteins. Pre-analytical factors that affect postmortem biospecimen quality vary across each assay and analyte combination, and relatively few formal studies have been carried out to understand these factors in detail. RNA, for example, is a relatively labile molecule that is subject to rapid degradation, so the integrity of RNA extracted from frozen postmortem biospecimens has traditionally served as a surrogate for overall biospecimen quality and suitability for genomic, proteomic, and other analyses.^{18–20} Factors affecting RNA quality in postmortem brain tissue are the most extensively studied, and results suggest that acceptable quality may be obtained 24 hours or more postmortem,²¹ although agonal and other antemortem factors (hospitalizations, respiratory illness, use of artificial ventilation, hypoxia, coma) may be as important as postmortem factors.^{20–28}

Ethical and regulatory best practices

Ethical and regulatory best practices relevant to postmortem biospecimen recovery for research include donor and next of kin consent, ethical procurement and use of postmortem biospecimens, and regulatory process oversight. Antemortem consent given by the donor and postmortem authorization given by the deceased donor's next of kin are the standard forms of consent obtained for postmortem biospecimen donation for research.

In the U.S., state law determines who can make an anatomical gift, how, and for what purposes. Practitioners should ensure that the wishes of individuals who make an anatomical gift while alive are honored and carried out. When the deceased did not make an antemortem anatomical gift, the consent given by the next of kin should be reasonable in scope, appropriately designed, and carried out to ensure the dignity of the deceased individual and their next of kin.

Although Title 45 of the Code of Federal Regulations (45 CFR part 46) from the U.S. Department of Health and Human Services regarding the protection of human subjects does not legally require that consent for research use of biospecimens be obtained from deceased individuals,²⁹ it is the recommended best practice to obtain the donor's antemortem consent, when possible, or the next of kin authorization for donation. In most instances when the individual has made a gift, the recovery agency will contact the next of kin to advise him/her of the donation and obtain additional medical and behavioral information. If the decedent did not make a gift, the reasonably available next of kin (as defined by state law) can authorize donation postmortem. Forty-three states have adopted the Revised Uniform Anatomical Gift Act of 2006 (RUAGA),¹⁵ which mandates that the deceased individual's wishes to donate/refuse to donate must be respected and that if the deceased individual made a gift (or refused), no other person may revoke or amend that gift.

The following issues may be particularly relevant to the consent/authorization process for postmortem biospecimen donation for research and should be clearly described when applicable:

- Risk of loss of privacy and confidentiality
- Future unspecified research use of donated biospecimens

- Extensive genomic and other molecular characterization of biospecimens that may have privacy and confidentiality implications for the donor and genetically related family members
- Treatment of some tissues and cells such that they may be maintained in a laboratory for an extended time
- Potential collection of a much larger quantity of tissue than in a typical autopsy

Best practices should allow for the donor or next of kin to withdraw consent/authorization for use of biospecimens in research. Biorepositories should develop policies and standard operating procedures for handling withdrawal of consent/authorization that reflect the language in the consent/authorization documents. The consent/authorization documents for donation of research biospecimens should clearly state who should be contacted to withdraw consent/authorization. The consent/authorization should also clearly state what will happen in the case of withdrawal and specifically any limitations to the ability to withdraw. Data associated with the donor may or may not also be withdrawn, depending on the type of data, the nature of the research project, the language in the consent document and the policies of the specific biorepository. In general, upon notification of withdrawal of consent/authorization, most biorepositories will remove and destroy all remaining biospecimens from the specified donor stored within the biorepository. Biospecimens that have already been distributed or used for research cannot generally be retrieved.

Ethics review varies by institution. In the United States, federal regulations define human subjects as living human beings; thus, the legal requirement that all human research undergo IRB review does not extend to research with the deceased.²⁹ The Consensus Panel on Research with the Recently Dead, however, recommends review by a multidisciplinary panel to address the distinctive ethical issues involved.¹² Best practices assert that postmortem biospecimen collection should receive formal ethics review to ensure that the collection is properly and respectfully conducted and the biospecimens and data are used appropriately. While not legally required, it is recommended that such a committee approve all protocols involving research biospecimen collection and that the committee certify that ethical concerns have been addressed.^{30–34}

Considering the donor family and the community

To honor donor and family wishes for funeral arrangements, OPOs, TROs, and RA programs seek to preserve donor body integrity as much as possible. Various techniques and biospecimen recovery approaches ensure that the donor's body is restored in a way that is suitable for funeral and burial arrangements. Direct cremation of the donor's remains typically can accommodate more extensive recovery of research biospecimens.

After each donation is received, the recovery organization should offer the donor's family gratitude and sympathy, bereavement resources, and information about some of the research programs that may use the biospecimen. Most organizations that conduct research using donated biospecimens have a policy of not returning research results to the donor and/or his/her next of kin though practices in this area are evolving.

Public perceptions of organ and tissue donation can be influenced through public education and media campaigns with the primary goal of conveying the importance of signing up to be a donor. The crisis of organ shortages in the United States helps to drive most local and national public education and media campaigns. National efforts have shown that knowledge and understanding of the need for donors increase the rates of donor designation, thereby increasing authorization rates for organ and tissue donation for transplantation, research, education, and therapy. Moreover, most religious traditions and cultural views support organ and tissue donation for transplant as a charitable act of love and giving,³⁴ in some cases, these views can be interpreted to include research use.

Conclusion

Postmortem biospecimens can be an important source of normal biospecimens suitable for a broad array of research applications to support scientific discovery. With a proportionately higher potential yield in biospecimen quantities from a single donor than with surgical tissue recovery, postmortem biospecimens may help relieve some current constraints on biospecimen-based research and therefore have an important impact on the development of new diagnostics and therapeutics. The *Recommendations for Postmortem Recovery of Normal Human Biospecimens for Research* (<http://biospecimens.cancer.gov/resources/oe/pr.asp>) provides a framework for collecting normal control biospecimens from postmortem donors. Awareness of these best practices can foster more effective collaborations, mitigate potential logistical challenges, and ultimately generate value from the dual goals of promoting postmortem biospecimen donation options for families and meeting the ongoing needs of researchers. With a strong ethical approach, proper program design, appropriate resources, willing and skilled sourcing partners, and good project management, a post-mortem biospecimen acquisition program can contribute significantly to the research enterprise.

Disclosure Statement

No competing financial interests exist.

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