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The National Disease Research Interchange and Collaborators on: What Are the Major Hurdles to the Recovery of Human Tissue to Advance Research?

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A standardized method to reduce analytic variables for the collection of human tissue is essential for investigators seeking to advance findings from basic disease research to new therapies for patients. When designing experiments involving human tissue samples, researchers must define specific donor criteria and preservation requirements useful for their analysis. Access to tissue from donors who fit specific criteria can be problematic if the donor profile or disease is not widespread. The biggest challenge facing human tissue research is identifying a significant number of donors who match specific eligibility criteria to add value to studies seeking cures or treatments for devastating diseases. Both diseased and nondiseased tissues are needed for comparison to understand the mechanisms of dysfunction, to seek potential biomarkers, or to evaluate potential therapies for disorders. The key to mitigating the challenge facing human tissue research is establishing a wide donor screening and recovery network to maximize donation opportunities that meet donor eligibility requirements and tissue collection parameters. The National Disease Research Interchange (NDRI) has developed several novel approaches to serve these specific scientific needs. To support uniform human tissue collection programs, NDRI has become accredited by the College of American Pathologists as a biorepository to enhance the reproducibility of our recovery network.

One method that NDRI uses to capture these very important human biospecimens is partnerships with organ procurement organizations (OPOs) for the screening and recovery of donors throughout the United States. The landscape of organ and tissue donation for transplant has changed significantly in the past 35 years, which has led to great opportunities for human tissue research efforts. Following the National Organ and Transplant Act passed by Congress in 1984, the Organ Procurement Transplantation Network was established to manage the organ matching process at 58 OPOs throughout the country. Currently, about 1.4 million deaths that occur in acute clinical care settings in the United States are referred to these OPOs for consideration for transplant. As not all organs and tissues from these donors are eligible for transplant, there are opportunities for donation of tissue for research through

the same mechanism. The NDRI, a 501(c)3 not-for-profit, uses the extensive screening and authorization in place at the OPOs to provide high-quality, highly annotated, nondiseased, and diseased tissues for research.

This recovery model has allowed NDRI to contribute to multiple large-scale NIH projects, including the Genotype-Tissue Expression (GTEx) project, through which NDRI collected 88,000 highly annotated tissue samples over 6 years. NDRI has established partnerships with a network of tissue source sites (TSSs) that include tissue banks, eye banks, hospitals, and recovery personnel, in addition to the OPOs, which all contribute to enhance the donor screening and recovery for tissues and organs for research. NDRI has established training programs and screening tools that have added to the success of these partnerships for the recovery of tissues for research. Using this nationwide network, essential for the identification and recovery of tissues needed for research, NDRI has supported the establishment of biobanks or assisted in addressing gaps within existing biorepositories, which are a critical resource for the scientific community.

Another approach is used by researchers studying rare diseases, by which a different model of donor identification and tissue collection is often necessary. There are more than 7000 rare diseases, defined as a disease that afflicts less than 200,000 patients a year in the United States. Studies evaluating treatments for these “orphan” diseases face the challenge of having access to human tissue from a very small segment of the population. Patient registries and education about the importance of donation for research are key to obtaining these valuable tissue samples. Patient registries allow contact with the donor and next of kin throughout life. The advantage to this approach is the opportunity to document clinical data over the course of treatment to enhance annotation of the biospecimen. A major challenge for these donors is facilitating the recovery of samples *post mortem* for patients who could be located throughout the United States. NDRI makes significant contributions to rare disease research through its Private Donor Program. In addition to tissue collection, NDRI has the capability to authorize donors for consent of tissues, either surgical or *post mortem*, for research use and the ongoing maintenance of donor registries. The Private Donor Program has served as a resource for organizations establishing a patient registry or by adding to their existing tissue collection.

Addressing the Needs of Neurological Biobanks

The issues facing tissue recovery for biobanks cross multiple scientific disciplines. NDRI’s recovery network and expertise are being deployed to enhance important tissue collections.

Diseased neurological tissue collection

NDRI has partnered with multiple foundations in support of its biobank collections, including neurological biobanks. These include partnerships with the Agency for Toxic Substances and Disease Registry’s (ATSDR’s), National Amyotrophic Lateral Sclerosis (ALS) Biorepository, contracted by McKing Consulting Corporation (McKing), and the Veteran’s Administration Biorepository Brain Bank (VABBB) for the collection of tissues from donors with ALS. ATSDR and VABBB use their own registry of patients for collection of clinical specimens and partner with NDRI for the recovery of tissues *post mortem*.

Recently NDRI partnered with the Children's Tumor Foundation (CTF) to authorize neurofibromatosis (NF) donors for the collection of tissues, using the Private Donor Program as a resource. Both ALS and NF are complex central nervous system disorders and the biobanks are collecting various tissues from each donor. NDRI works with each organization to develop customized protocols for the recovery of tissues that fit their collection requirements, ensuring the successful collection of quality samples needed for studies evaluating treatments for these rare neurological diseases.

Selective eligibility screening for neurological tissue collection

In 2015, NDRI received funding from two organizations seeking to expand their donor screening efforts for tissues difficult to obtain in the general population. The National Institutes of Mental Health provided funding to NDRI to obtain brains from donors with autism spectrum disorder (ASD), as well as from normal controls aged 2–18 years. In addition, NDRI received funding from the Henry Jackson Foundation on behalf of the Center for Neuroscience and Regenerative Medicine at Uniformed Services University of the Health Sciences to collect brains from donors aged 18–60 years who have U.S. military service history. This collection will be used to study the impact of military service on traumatic brain injury (TBI). These are not "diseased" donors, but who have the potential to address important questions about the risk of TBI in the military. A donor registry model would not adequately serve these initiatives, as neither autism nor TBI leads to the death of these patients. NDRI contributes to these projects by expanding its reach to maximize donation opportunities. NDRI relies on relationships with OPOs and tissue banks to approach next of kin for consent. NDRI has successfully performed outreach to inform recovery organizations and personnel of the importance of human tissue for research, increasing the successful conversion of these referred cases to recoveries for the biobank.

Summary

The need for well-preserved human tissue is essential for studies seeking to identify cures or new treatments for diseases. Identifying donors as quickly as possible after death and working with trained recovery personnel are critical for obtaining specimens for biobanks that can be useful for researchers working to expand their preclinical work to human tissue. Neurological biobanks are one example, but this is true for other research areas as well. NDRI's nationwide TSS network is an effective resource for researchers, allowing for identification of targeted donor populations and timely collection of samples. Whether working with existing patient registries or seeking to identify eligible donors, NDRI lessens the challenges facing tissue collection efforts.

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The National Institutes of Health NeuroBioBank

Federal agencies and private foundations invest heavily in research studies designed to reveal the genetic and environmental underpinnings of ASD to provide targets for potential therapeutic intervention and to develop a better understanding of risk factors that may contribute to disease susceptibility. Advances in genomic technologies facilitating RNA and DNA sequencing, coupled with advances in high-resolution imaging, have led to a myriad of scientific opportunities that are primarily limited by a shortage of available *post mortem* brain tissue. Owing to the increasing prevalence of individuals diagnosed with ASD and the relative paucity of human scientific research on these disorders, *post mortem* brain tissue from this population is among the most highly sought after resource from brain banks. However, as young children with autism do not typically die from chronic diseases, but instead die from accidental causes, arrangement for brain and tissue donation is often not considered before death, making the consent process all the more challenging.

Historically, ASD tissues for research have been made available through two sources: the University of Maryland Brain and Tissue Bank, formerly known as the NICHD Brain and Tissue Bank for Developmental Disorders, and the Autism Tissue Program, a program managed by Autism Speaks. Both of these programs have evolved in recent years and are now components of different programs, the NIH NeuroBioBank and Autism BrainNet, respectively.

These two entities are working together to align procedures used to collect, prepare, and preserve ASD tissues. Autism Brain NET is focused exclusively on the collection of ASD-related donors and controls whereas the NIH NeuroBioBank has a much broader disease scope.

The NIH NeuroBioBank was established in 2012 as a federally funded resource for the scientific community studying human neurological, neuropsychiatric, and

neurodevelopmental diseases and disorders. This resource was created with the goal of increasing the availability of high-quality *post mortem* human brain tissues across a broad spectrum of neurological diseases and disorders, and of capitalizing on the economies of scale gained over previous funding and organizational models. In addition, the NIH NeuroBiobank aims to increase public awareness about the value of human tissue donation for research by providing web-based information and through active outreach to disease advocacy communities.

Successful acquisition of *post mortem* human brain tissue for research has many obstacles to navigate, in particular, public awareness of the need for such tissues. Although the general public is quite familiar with the need for organ donation for transplant purposes and even for research; nonetheless, the concept of brain donation for research is somewhat unusual to most, thus underscoring the need to promote the value of research supported by human brain donation. There are several advocacy organizations that work to educate and engage parents about the importance of brain/tissue donation and to preregister potential donors. Despite preregistration, there are a number of challenges associated with successfully retrieving a brain donation. Despite indicating an interest to donate, consent must be obtained from the next of kin at time of death. A brain bank must be willing to accept the donation as well as provide the means to retrieve the brain within a relatively narrow time frame after death. A number of exclusion criteria must be enforced to ensure high-quality tissue for research studies. This involves compassion and sensitivity when approaching the family of a recently deceased individual and oftentimes considerable postdonation follow-up, including extensive review of medical records and possibly interviews with the family.

In addition to the need for ASD donors, there is a considerable paucity of age- and sex-matched unaffected controls and family members required to conduct scientifically rigorous research studies. Young unaffected controls are an especially difficult group to acquire, as families are unlikely to have considered brain donation before the death, and are often unable or unwilling to consider this during their time of grieving. In addition, these cases often come through the medical examiner or county coroner’s office, which very rarely consent families for brain donation as a matter of routine, highlighting the need to establish working relationships with these very important colleagues. Once a strong relationship is formed, the lines of communication are more open to authorize contact with the family for consent.

NDRI has developed extensive relationships with OPOs and has been working with them for more than 25 years in the accession of multiple tissues for research under an NIH-funded program, The Human Tissue and Organ Research Resource. This program has allowed NDRI to establish a strong collaborative network throughout the country, facilitating access to rare and highly desired specimens for research. Several years ago, NDRI was subcontracted to manage the collection of human *post mortem* brains for the GTEx project, an NIH-funded program that aims to provide to the scientific community a resource with which to study human gene expression and regulation and its relationship with genetic variation. NDRI’s involvement in this program allowed it to develop standardized protocols for brain collection and shipment to the contract site responsible for handling the *post mortem* brains, putting them in a unique position to help the NIH NeuroBioBank increase

the number of donors with ASD and control brains in the collection. We began a pilot program with NDRI, providing it with resources to establish the necessary screening and consent tools required for collection through many of its partner organizations. This development phase required considerable effort to define and create standard operating procedures (SOPs) specific to this unique population. Initial goals for the NDRI/NIH NeuroBioBank collaboration are to collect 15 donors with ASD and 15 young unaffected controls per year. Initial results are promising and we are optimistic that these goals will be realized in the coming year.

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The National ALS Biorepository

ALS was first described in the 1800s but little is known about its cause(s) or how to treat it. The single approved medication for ALS, riluzole, extends life for only a few months and treatment is otherwise limited to supportive care. For many years, clinical investigations of ALS consisted mostly of small case series. Because ALS is rare, it remains challenging to identify sufficiently large and well-characterized groups of affected people for research on its causes, natural history, and potential prevention and treatment. Progress toward this end includes the development of standardized diagnostic criteria, multicenter clinical databases, and population-based registries. Research on the underlying pathobiology of ALS has long relied mostly on *post mortem* examination of neural tissue. During the last decade, however, advances in molecular and imaging technologies have vastly expanded the range and quantity of biological information available for ALS research.

A number of pressing questions about ALS remain unanswered. These include the following: What are the underlying causes? How can understanding these causes lead to prevention and treatment? What biomarkers are useful for predicting disease progression and treatment response? Answering these and other important questions requires the integration of epidemiological, clinical, and basic research findings to suggest hypotheses and provide a

basis for inference. The best opportunity to bridge this gap is to collect and bank biological specimens from participants in the congressionally mandated National ALS Registry (Registry), a population-based registry maintained by the Agency for Toxic Substances and Disease Registry (ATSDR), a federal public health agency of the U.S. Department of Health and Human Services. Registrant biospecimens are collected in a biorepository that complements the Registry's epidemiological data and also adds to the total number of biological specimens available for research on ALS.

The pilot study

In 2011, McKing was awarded a contract by ATSDR to conduct a pilot study to determine the feasibility of establishing a biorepository of specimens to complement the Registry. Participants in the study were recruited nationwide from persons participating in the Registry. Three hundred thirty participants were enrolled in the biospecimen donation (blood, urine, hair, and nails) part of the study. DNA and RNA were extracted from blood samples. Owing to the limited mobility of persons with ALS, our primary method for obtaining blood and urine specimens was by an in-home visit from mobile phlebotomists. The pilot study was structured to complete two in-home collections at 6-month intervals; however, ~20% of participants were unable to complete the second collection mostly because of death or disease progression. This pilot study also included *post mortem* tissue collection—whole brain, spinal cord, cerebrospinal fluid (CSF), bone sample, muscle sample, and skin sample for dermal fibroblast cell development. Thirty participants in 18 states were enrolled in the *post mortem* part of the study.

Challenges of post mortem tissue collection

The purpose of the ALS Biorepository Pilot Study was to test the feasibility of conducting population-based specimen and tissue collections from participants in all 50 states and in both urban and rural settings. With such a large geographic coverage, knowledge and understanding of the individual state laws that govern *post mortem* tissue donation and retrieval were extremely important. In addition, the goal was to recover tissues within 24 hours of death and deliver to the project's neuropathologist at Boston University within 24 hours of collection. To accomplish this, McKing needed a partner with an established network of qualified dieners across the United States who would be able to ensure standardized tissue collection, advise McKing throughout the project, and quickly resolve any issues that came up during the *post mortem* tissue collections.

NDRI's role

McKing partnered with NDRI to plan for and conduct the *post mortem* tissue retrieval (whole brain, spinal cord, CSF, muscle, bone, and skin). NDRI established SOPs for the tissue collection and trained each of the dieners on the SOPs. For each participant, NDRI identified and contracted with a primary and backup local diener, predeployed a custom collection kit to the primary diener, identified a collection facility, and arranged for transportation of the donor to and from the donation facility. Over the past 3 years, NDRI has maintained contact with all of the primary dieners throughout the project to reconfirm their availability, confirm the accessibility of the collection kits, and discuss upcoming planned absences by which a backup diener might be needed. This advance planning

allowed McKing to adhere to the study standard of collecting tissues within 24 hours of death for ~80% of the tissue retrievals. As of August 2016, NDRI has assisted McKing with 19 *post mortem* tissue retrievals across the United States.

The future of the National ALS Biorepository

Upon successful completion of the pilot study, ATSDR decided to move forward with establishing a National ALS Biorepository. McKing was awarded a contract in 2015 to support ATSDR in ongoing specimen collections. Over the next 4 years, McKing will continue the in-home collections, enroll 40 new participants for *post mortem* tissue donation, and will complete the *post mortem* collections on the remaining participants from the pilot study. McKing has again partnered with NDRI for the *post mortem* tissue retrievals.

The National ALS Biorepository will make biological samples and tissues available to approved researchers and has begun to distribute those collected during the pilot study. ALS researchers interested in obtaining biological samples or tissues for their research must submit an application to ATSDR and have the research approved. For more information on how to make a request, researchers can visit the National ALS Biorepository website: (wwwn.cdc.gov/als/ALSNationalBiorepository.aspx).

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CTF Biobank

Accelerating research and development of novel drug treatments depends highly on the discovery of new disease mechanisms. This is especially true for rare diseases such as NF.

NF is a family of rare genetic conditions (NF1, NF2, schwannomatosis) that affects ~1:2500–3000 births. It can cause manifestations including neurofibromas (plexiform, cutaneous, and atypical), low-grade gliomas, bone issues, learning disabilities, malignant tumors (breast, MPNST, GIST), schwannoma, and meningioma.

The protean nature of these rare disorders has led to the lack of sufficient tissue per manifestation to identify novel drugable disease targets.

Moreover, although the overlap in molecular pathways between NF and cancer leads to highly valuable drug repurposing opportunities, the toxicity profiles of some oncology drugs may not be ideal for long-term therapy.

Therefore, the availability of high-quality human tissue to all qualified researchers, not just those at major institutions housing private biobanks, becomes essential to the discovery of novel targets and treatments.

Until recently, patients who wished to donate tissue specifically for NF research had no way to do so, unless they were treated at an institution that has the ability to accept body donations.

The CTF identified the need for an open-access biobank to both expand research opportunities and to engage patients and give them hope for the future and a positive attitude toward medical research.

In May 2013, CTF obtained Institutional Review Board approval for its first collection protocol: The Collection of Surgical Discards of Dermal Neurofibromas from Patients with NF1 for Research Purposes. We chose cutaneous neurofibromas as our first biobank project for two reasons: (1) because the tissue was available through a collaboration with a private plastic surgeon, who arranged for CTF personnel to collect the dermal neurofibromas at his facility, and (2) because this type of tumor is significantly understudied and the research community could highly benefit from full characterization of these tumors.

The Foundation has collected more than 100 cutaneous neurofibromas along with patient-reported NF medical histories. Both tissue and data are stored at Precision Bioservices

(Frederick, MD). Full “omic” characterization of 50 samples was outsourced to the Genomic Services Laboratory at HudsonAlpha Institute for Biotechnology (Huntsville, AL). After data analysis at Sage Bionetworks (Seattle, WA), the data are now openly available to the research community (www.synapse.org/#!Synapse:syn4984604/wiki).

Before expanding the biobank to include other tissues, the Foundation identified the need for a biobank summit to develop agreed-upon NF-specific SOPs for biobanking, based on the NCI Best Practices for Biospecimen Resources (https://biospecimens.cancer.gov/practices). The outcome of the summit was published in *Neurology Supplement* 2016:87 (7 Suppl. 1: S40).

With the success of this pilot project, the Foundation decided to take on a much bigger challenge: meeting the requests of members of the patient community to donate postmortem tissues specifically for NF research.

The major challenge in this endeavor was to find a partner who could:

- provide a full service, from patient to tissue,
- collaborate with CTF in maintaining participant data in a shared database,
- be permanently available (24/7) across the country,
- be flexible to customize collection of the most relevant tissue per any given patient,
- guarantee the collection of high-quality, well-annotated tissue in our biobank, and
- guarantee shipping of the recovered tissues to multiple recipients within a very tight time window.

The partner who met all the mentioned criteria was NDRI because it has an excellent track record of *post mortem* tissue management and the team was willing to collaborate with CTF to develop a rather complex flowchart.

We developed a flowchart to allow:

- IRB-approved informed consent for body donation and collection of medical records,
- referral to NDRI for logistics around the time of death, minimizing the recovery time (<24 hours),
- validation that the tissue is NF relevant by an NF-trained pathologist, and
- creation of new cell lines for NF research.

In the current protocol, CTF acts as the connector to the patient community. Any patient who is interested in donating his or her body to NF research reaches out to the clinical program director of the Foundation, who performs the screening and consent process. CTF collects and extracts relevant clinical data from the medical records, manages a premortem blood collection, and maintains a close relationship with the patients.

A member from the NDRI team, alerted by CTF, contacts the patients and their families to develop a mutually agreed-upon, thoughtful plan for body recovery.

At the end of life of the patient, CTF and NDRI effectively collaborate to streamline all the necessary activities that are needed to guarantee top-quality tissue in the biobank.

CTF has been very impressed with the level of flexibility that NDRI has demonstrated to make sure no collection opportunities are missed. To date, this collaboration has resulted in efficient recovery of tissue from four deceased patients.

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