

# Sculpting the Future of Biobanking Base by Base

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**H**UMAN BIOSPECIMENS CONTINUE to be an essential resource for the scientific community to understand disease etiology as well as translate pre-clinical findings into diagnostics and therapeutics across the disease spectrum. Access to suitable biospecimens can be challenging for investigators, making biobanks and tissue procurement organizations valuable partners for a wide range of research aims.

Significant advances have been made in the past ~20 years in genomic and transcriptomic experimental methodologies that allow investigators to detail tissue-specific, and more recently, single-cell gene expression profiles that are providing insight into the impact of genetic variation on human disease and patient-specific treatments. To support these new and emerging experimental methodologies, it is paramount that biobanks and tissue procurement organizations continue to evolve at equivalent measures to provide suitable samples to investigators through expert technical and ethical practices.

The National Disease Research Interchange (NDRI) has been serving the scientific community for >40 years through the distribution of human tissues to investigators. Detailed here is NDRI's perspective on current advancements and considerations for how biobanks and tissue procurement organizations can meet the progressing landscape of needs that are facing investigators today.

## Supporting the Evolution of Genetic Sequencing Data

From the impetus of genome-wide association studies identifying association of genetic variants and human disease, it has been clear that the complexity of the human genome requires more specific and detailed methodologies to identify how these variants impact gene expression and disease pathology. The first large step was undertaken by the National Institutes of Health (NIH) Common Fund's Genotype-Tissue Expression (GTEx) project. This project, initiated in 2010, was a groundbreaking initiative that established the first comprehensive public resource correlating gene expression and genetic variation in the adult population by using expression quantitative trait loci mapping to provide cellular context to variation in gene regulation.<sup>1</sup>

This effort required a large-scale tissue procurement endeavor where up to 35 tissues across body systems were collected from nondiseased post mortem donors (age >21 years) with low post mortem to preservation intervals. The innovative tissue collection methodologies that were de-

veloped by NDRI and the GTEx Consortia empowered the success of this innovative project. The emergence of RNA sequencing technologies at the height of the project and the extensive reference data set created have allowed GTEx to continue to yield fundamental scientific data for investigators, including but not limited to tissue-specific gene expression profiles and sex-related differences in gene expression profiles across the adult population.<sup>2</sup>

This successful tissue collection project provided the research community with proof of principle that high-quality samples suitable for rigorous reproducible data collection and genetic analysis could be derived from post mortem donor tissue, opening up a plethora of possibilities for future investigations. In addition, the language in the GTEx authorization for donation was designed to improve authorization practices by providing more informed, transparent descriptions to family decision makers on the scientific goals, tissue requests, and potential risks to the family for participating in the project. The GTEx standardized recovery methods and authorization language are still used as key benchmarks for developing best practice on current and future tissue collection projects.

## Combining Structural and Molecular Approaches to Address Cell-Specific Function

GTEx has provided a road map to understand genetic variation across tissues in the human body. However, other approaches are necessary to map individual cellular profiles within distinct tissues and define region-specific patterns and variation in cellular connectivity that lead to organ function and/or dysfunction. Several NIH-funded consortia have been addressing the mapping of specific organs, including the brain through the BRAIN Initiative Cell Census Program<sup>3</sup> and the lungs through the Molecular Atlas of Lung Development Program.<sup>4</sup>

These approaches include teams of investigators at multi-site research centers with extensive expertise across multiple experimental modalities. They combine imaging techniques to capture structural data of the whole organ as well as molecular techniques to thoroughly study individual cell types as isolated single cells or single nuclei as well as in native multicellular preparations. Instead of evaluating expression changes across the same individual, these organ-specific initiatives take advantage of specialized approaches to map organs from various developmental stages to identify

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changes in gene expression and function as organs develop. In addition, the LungMAP program served as a proof-of-concept model for utilizing pediatric organs and tissues to develop a groundbreaking research resource for the scientific community.

### Mapping the Human Body—Bold Outcomes from Single-Cell Molecular Methodologies

Since GTEx, the spatial resolution that is possible with genomic and transcriptomic methodologies, particularly with advances in the field of single-cell genome sequencing, has led to multiple initiatives aimed at creating reference maps of all human cells across tissue types. These initiatives include the Human Cell Atlas<sup>5</sup> and the NIH's Human Biomolecular Atlas Program (HuBMAP).<sup>6</sup> Both initiatives are focused on creating global collaborative investigator networks using cutting-edge omics technologies to map the human body at single-cell resolution and create three-dimensional maps of all tissues. This next stage of genomic research provides an exciting platform for organizations that can provide the community with access to healthy human tissues from all body systems.

The data that are being generated from these initiatives will shed new light on disease pathogenesis and allow investigators to identify specific cellular targets from complex phenotypes that will enable more rapid development of therapeutics and diagnostics. These initiatives to date, unlike GTEx, do not have a centralized source for tissue collection, which could be a risk for these programs. Variation in collection procedures could generate artifacts in the data and analysis using these highly sensitive experimental procedures, yielding potential rigor and reproducibility issues for investigators. Owing to the sensitivity of single-cell molecular methodologies, there is an utmost need to utilize best practice methodologies in tissue collection, handling, and shipping consistently for these applications.

### Important Considerations for Single-Cell Mapping and Biobanking Initiatives

A key component of the success of the cell atlas projects already described is the accessibility of the biospecimens collected as well as the genetic data derived from the samples, creating community resources where as much of the data generated are shared as possible, including genetic data that could be unique and identifiable. This presents ethical challenges that must be considered when collecting tissues for these efforts.

Although the collection of post mortem tissue is not considered human subjects research according to 45 CFR 46, the genetic information generated from the specimens could directly impact donor families, making informed consent a critical component of publicly accessible genomic studies. Key elements that should be included in donor authorizations include intention to perform genetic analysis, the data sharing methods to be used for the study (open access vs. restricted access), and the unknown future use of samples to be biobanked. Building on the GTEx authorization, NDRI has successfully developed and implemented project-specific authorizations that meet these criteria, without impeding the success of the programs.

Another ethical consideration that must be included in the experimental design is the return of results to donor families, an issue that is coming to the forefront as the number of data sets available for genomic analysis, such as those described here, increases.<sup>7,8</sup> The return of genetic results, particularly incidental findings, is best examined and defined for participants at the start of the project, with thoughtful consideration of the risks, benefits, and expertise of the research team. The Ethical Legal Social Implications (ELSI) study associated with GTEx highlighted the importance of clarification regarding the return of genetic results,<sup>9</sup> an important consideration for future studies.

### New Frontiers for Biobanking—Broadening to Encompass More Diverse Donor Cohorts

Although the GTEx project and the more recent single-cell mapping research initiatives have begun to compile critical reference data for healthy human tissues, gaps still exist for the tissue banks created for these projects and for investigators accessing these data sets. There is a critical need for access to tissues from diverse donor cohorts, including by geography, gender, age, and ethnicity. Most biobanking efforts have an oversampling of adult Caucasian donor tissues.

A focus on diversity, equity, and inclusion (DEI) in human tissue and cell mapping efforts will provide genomic data sets that most accurately represent genetic variation in health and disease for the global community. It is difficult for one initiative alone to take on the challenge to fill these gaps, but engaging stakeholders in DEI goals at the onset of tissue collection is key. NDRI is participating in a new National Human Genome Research Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Neurological Disorders and Stroke, and National Institute of Mental Health initiative, developmental GTEx (dGTEx), to expand the reference data sets collected by GTEx to the pediatric population.

Collecting a wide range of tissues from healthy pediatric post mortem donors across several age ranges for detailed molecular analysis will provide insight into tissue and cell-specific gene expression during development and in pediatric and adult-onset disease. This is a multi-institutional effort that includes experts in pediatric pathology and biobanking at Children's Hospital of Philadelphia, University of Maryland Brain and Tissue Bank and Johns Hopkins All Children's Hospital to serve as the Biospecimen Procurement Center (BPC) for the dGTEx initiative. In addition to providing samples for the dGTEx project, the BPC will conduct an ELSI study focused on enhancing DEI in pediatric biobanking studies, which may provide insights into approaches that can be used to more effectively engage diverse communities.

### Conclusion

As investigators become engaged in cell mapping initiatives and more public research resources with human sequencing data are developed and launched, lessons learned from the projects mentioned will strengthen the foundation for the next generation of human tissue biobanking and research resource efforts. Experimental methodologies and technologies will push beyond the single cells to subcellular sequencing and mapping initiatives. The proven approaches that have been essential in providing investigators with access

to high-quality biospecimens will need to hit the mark again to support the exceptional goal of improving our fundamental understanding of human genetics, biology, and physiology.

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