Applicant Information Webinar: Developmental Genotype-Tissue Expression (dGTEx)

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Applicant Information Webinar: Developmental Genotype Tissue Expression (dGTEx)

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Please note that this webinar will be recorded for internal NHGRI use only.

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Outline

- Background
- RFA Overview
  - Biospecimen Procurement Center
  - Laboratory, Data Analysis, Coordinating Center
- Key Dates
- Frequently asked questions
- Applicant questions

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NIH Collaborations

Trans-NIH Initiative

- Co-leads
  - National Human Genome Research Institute (NHGRI)
  - National Institute of Child Health and Human Development (NICHD)
- Co-contributors
  - National Institute of Mental Health (NIMH)
  - National Institute of Neurological Disorders and Stroke (NINDS)

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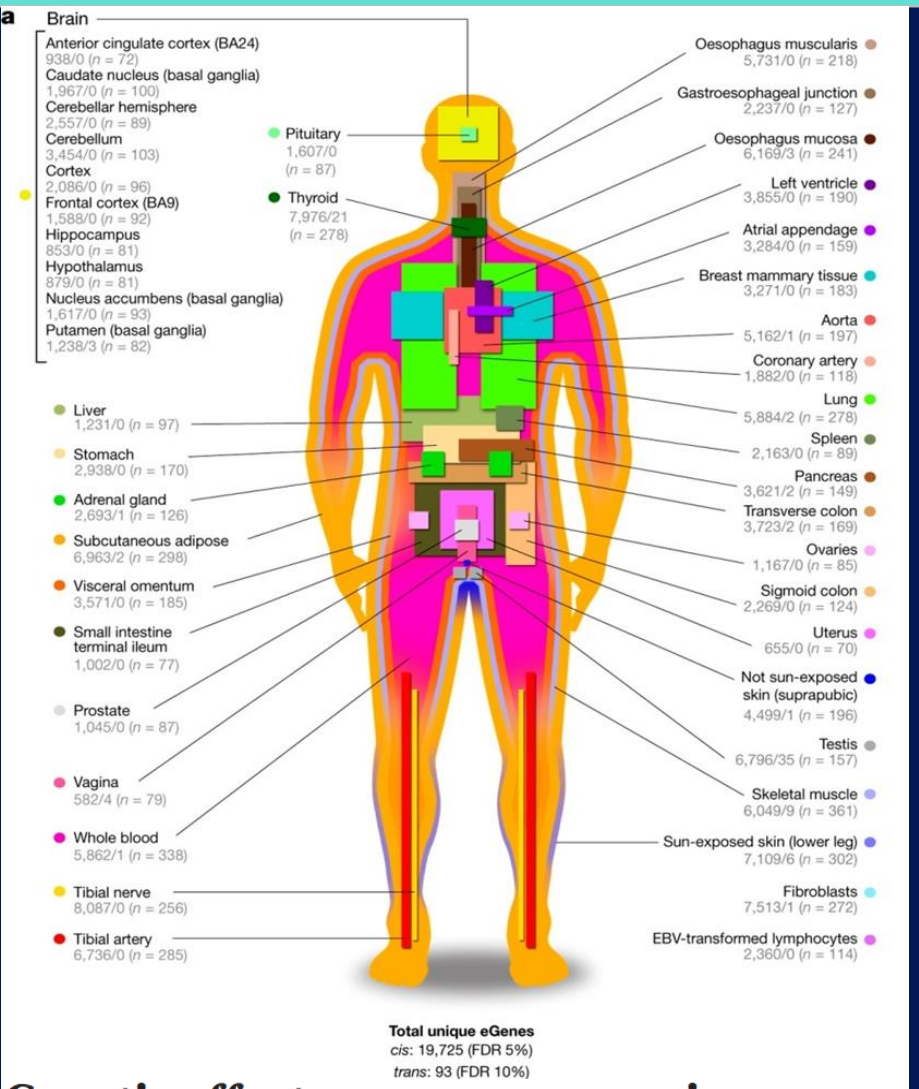
GTEx Accomplishments



Genetic effects on gene expression across human tissues

GTEx Consortium*

- Established rapid autopsy program
  - 965 donors (2010-2016)
- Surveyed gene expression in 53 tissues
- Provided new approach to map gene expression
- Decoded regulatory regions of genome

Over 2,000 consortium and non-consortium papers and 2nd most data access requests

Proposal: Developmental Genotype Tissue Expression (dGTEx)

Differences in Development

- Metabolism
- Endocrine function
- Immune function
- Drug response
- Exposure and susceptibility to environmental toxins

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Goal: Establish resource database to study gene expression patterns across developmental stages.

- Fill key gaps in understanding gene expression in human development
- Provide insight on functional networks and pathways
- Understand how gene expression affects clinical factors (ex. drug response)
- Explore attitudes/concerns family decision makers, cultural differences, consent process

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Objectives

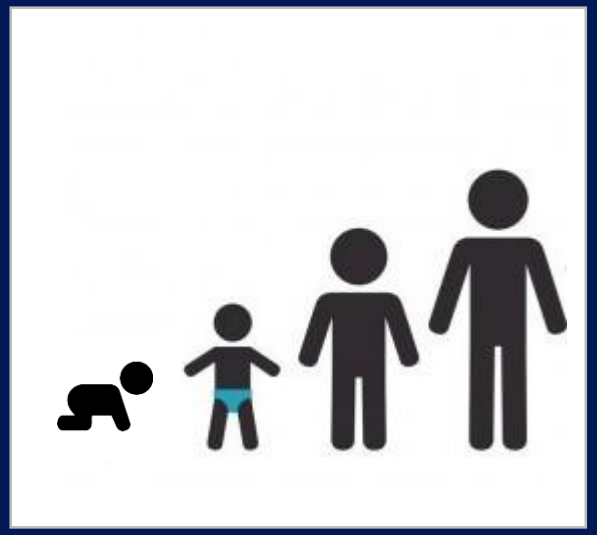
Create an atlas of tissue gene expression on bulk tissues and single cells in pediatric populations.

Analyze differences in gene expression, regulation, and known eQTLs and sQTLs across developmental stages.

Create and make available biobank of tissues and associated data for further characterization.

Develop research projects on the Ethical, Legal, and Social Implications of post-mortem pediatric genomic research.

Study Design



- Early postnatal (0-2 yrs)
- Early childhood (2-8 yrs)
- Pre-pubertal (8-12.5 yrs)
- Post-pubertal (12.5-18 yrs)

- Biospecimen collection (blood, bulk tissue)
- Assays (genomic, single cell)
- Special brain consideration

Future assays
- Chromatin accessibility
- Histone modification
- DNA methylation

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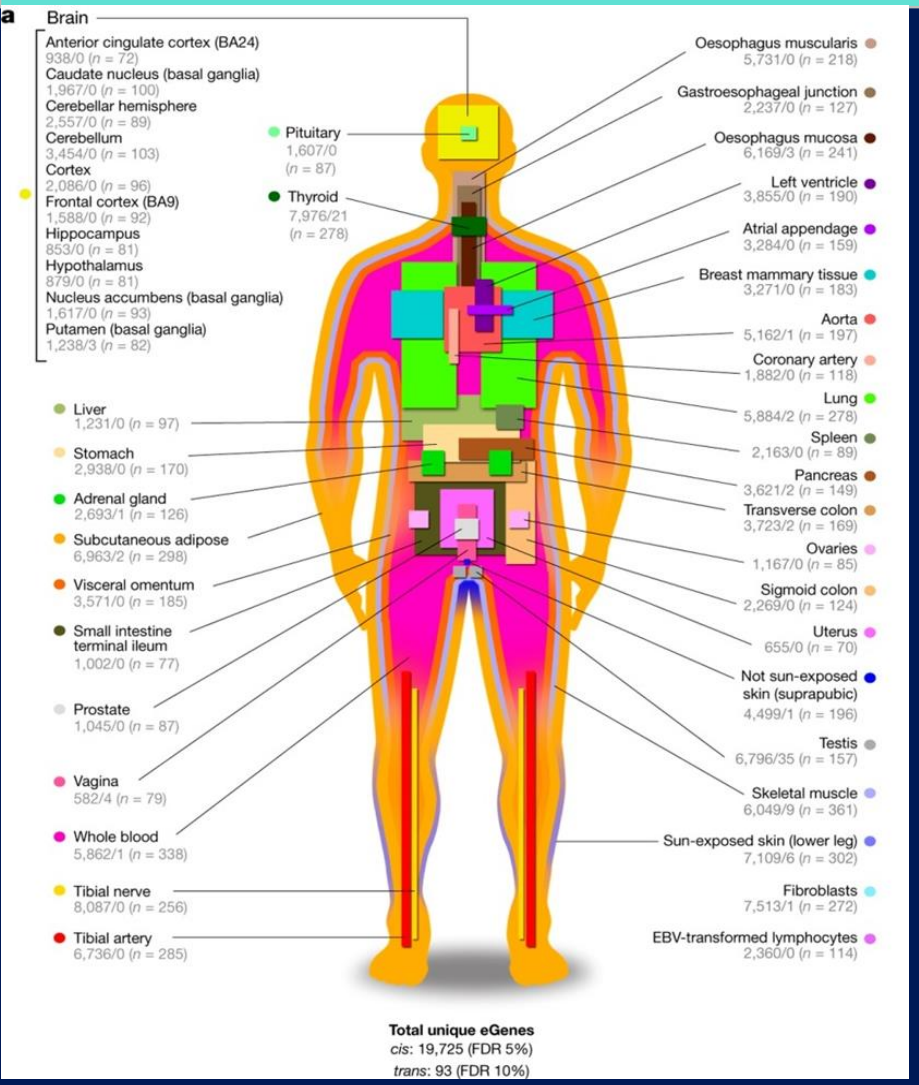
Tissue Procurement



- At a minimum, recruit 120 donors (at least 20-30 normal tissues per donor)
- Post-mortem tissues collected from neonates, young children, adolescents after acute event
- Collect as many tissues as possible similar to GTEx
- Prioritization of actual tissues collected determined by Steering Committee

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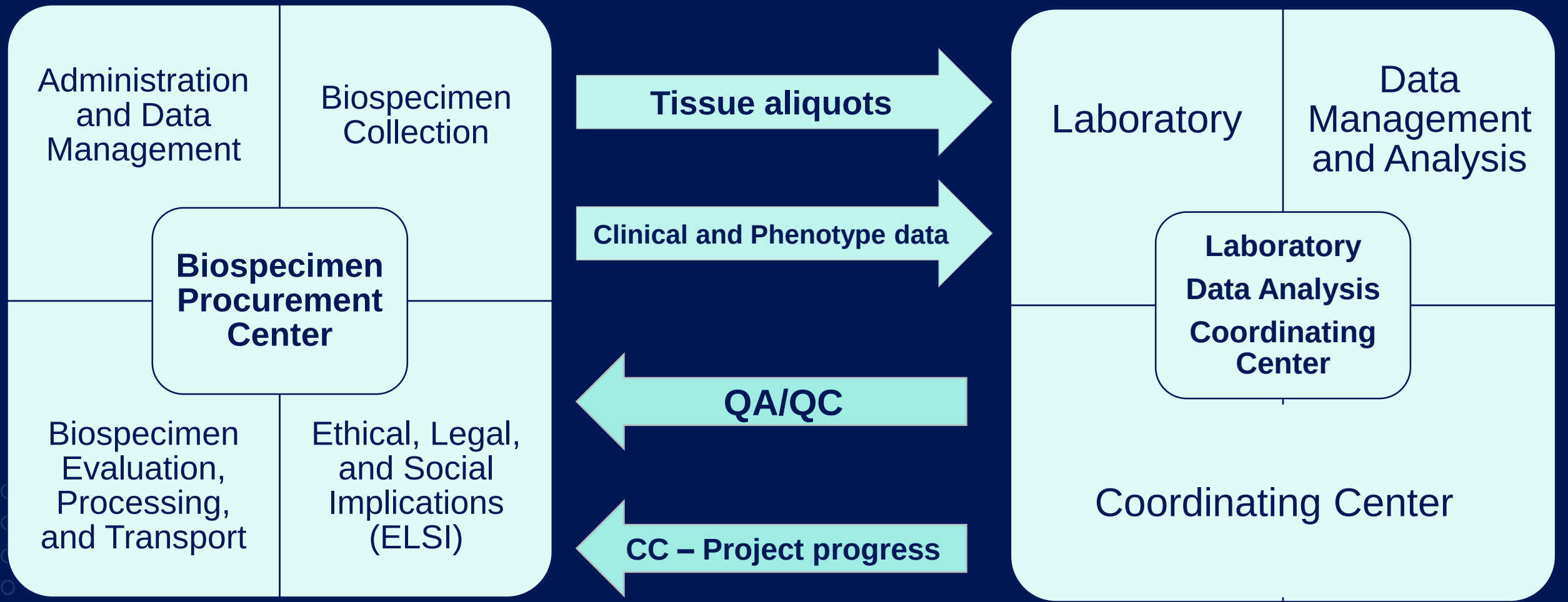
Special Consideration - Brain

- Tissue Procurement
  - Expert evaluation, precise dissection using a coordinate system or equivalent, and optimal preservation of brain tissue for single-cell data generation (optimally, PMI < 8hrs)

- Sequencing and analysis
  - Special expertise for processing tissue and generating and analyzing single-cell (~10 subregions) expression data
  - Standards compatible with Brain Initiative Cell Census Network (BICCN)

Consortium Organization



Program Formation and Governance

- Steering Committee
  - PIs from BPC, LDACC, NIH program staff
  - Oversees project goals and progress
- Community Advisory Board (CAB)
  - Convened by BPC investigators
  - Provide input on community concerns, strategies on outreach, education, and consent
- External Scientific Panel (ESP)
  - Convened by NIH
  - Provide scientific expert recommendations

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Data Collection and Sharing

- Data Collection
  - Informed consent include language that biospecimens and derived data to be shared and deidentified
- Broad sharing and research results
  - Genomic and other relevant data shared with scientific community for research → AnVIL
  - Institutional certification designated as General Research Use

Biospecimen Procurement Center Award

Award

- One award
- Cooperative agreement U24 mechanism

Budget

- Total cost $12.5M over the five-year budget period
- Total cost range $1.4M - $3.6M depending on year
- NICHD, NINDS, NIMH

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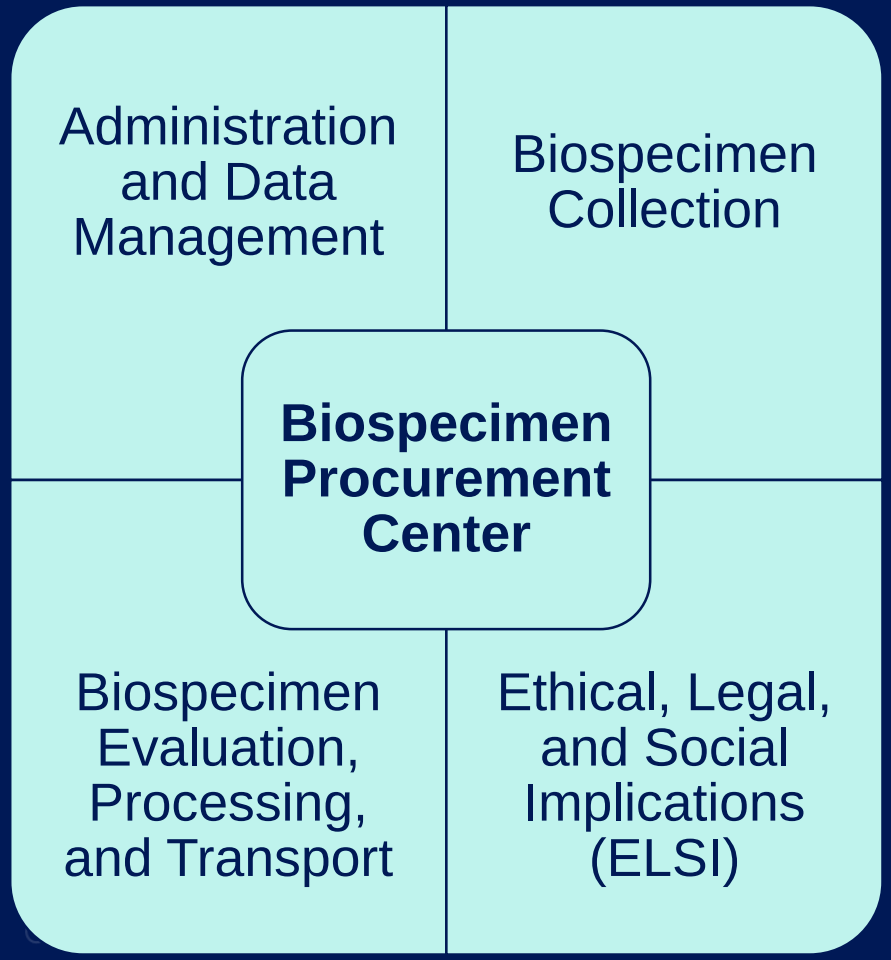
Biospecimen Procurement Center



Goal: Recruit 30+ donors from each age group

- Early post-natal (0-2 years)
- Early childhood (2-8 years)
- Pre-pubertal (8-12.5 years)
- Post-pubertal (12.5 – 18 years)

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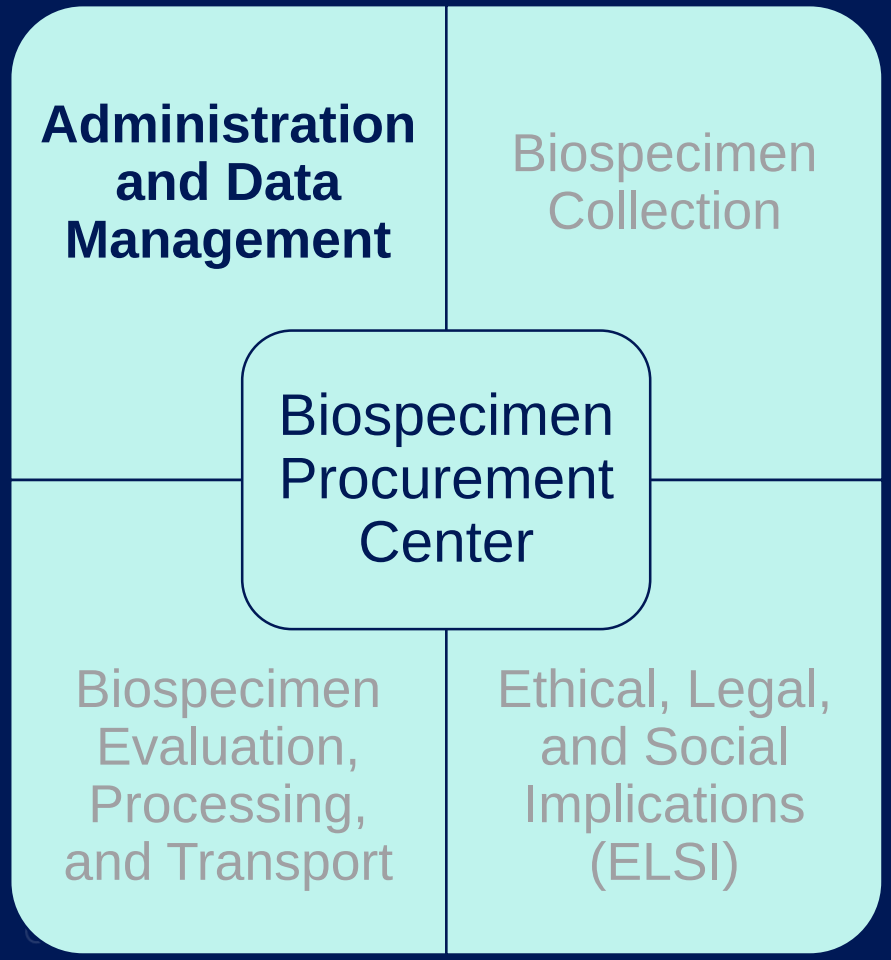
Biospecimen Procurement Center



Administration and Data Management

- Oversight for BPC
- Manage entire biospecimen procurement project

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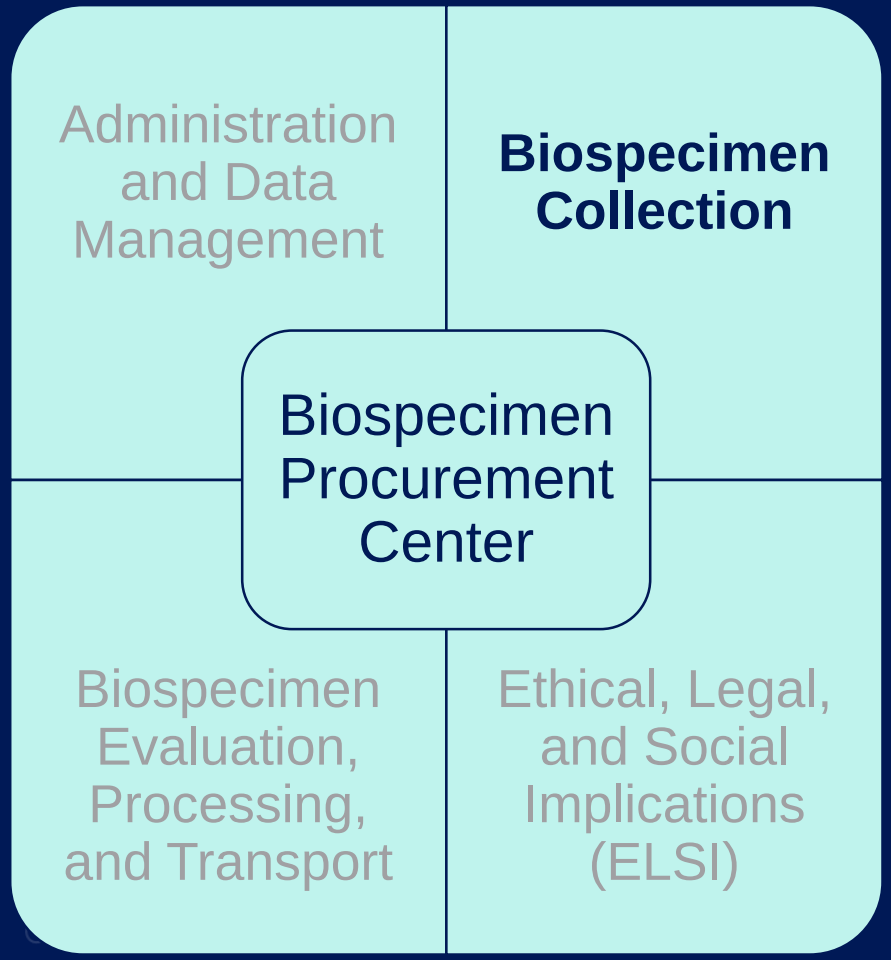
Biospecimen Procurement Center



Biospecimen Collection

- Coordinate biospecimen procurement from numerous tissues and associated clinical data from donors
- Collaboration with multiple tissue source sites (TSS) will be required for meeting the procurement goals (e.g., organ donor organizations and medical examiners)

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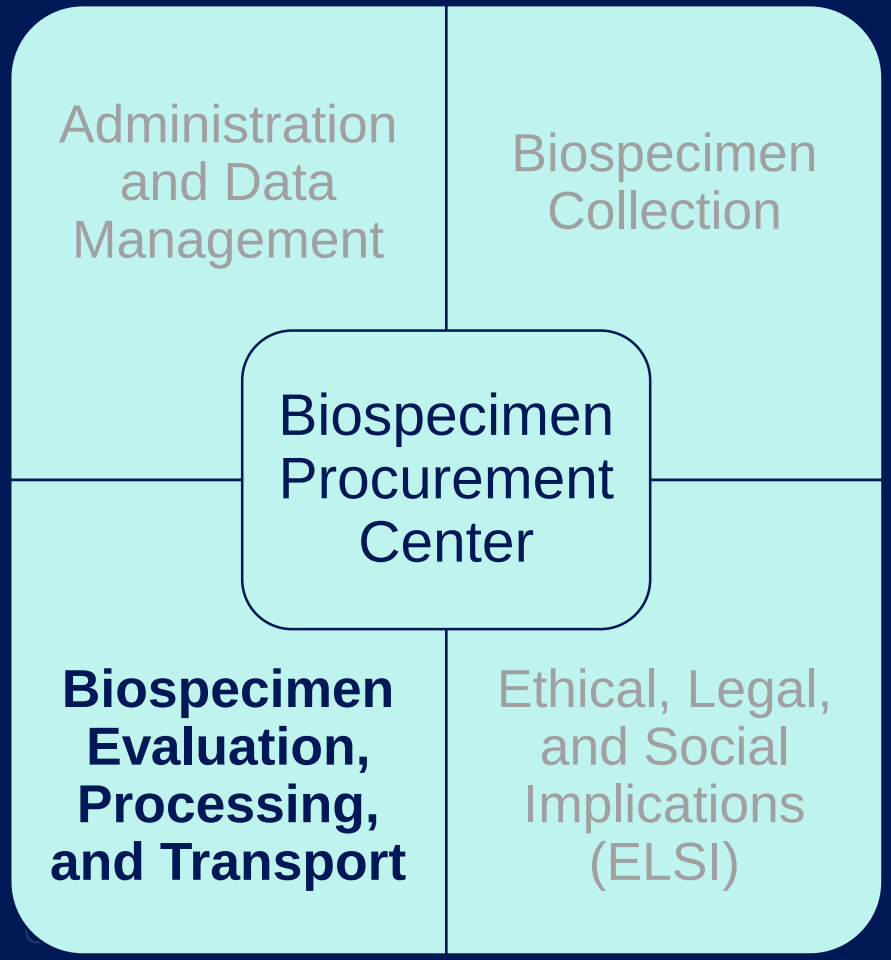
Biospecimen Procurement Center



Biospecimen Evaluation, Processing, and Transport

- Optimize tissue collection
- Provide standardized collection kits for biospecimen collection
- Pathological review of organ source
- Ship samples to LDACC

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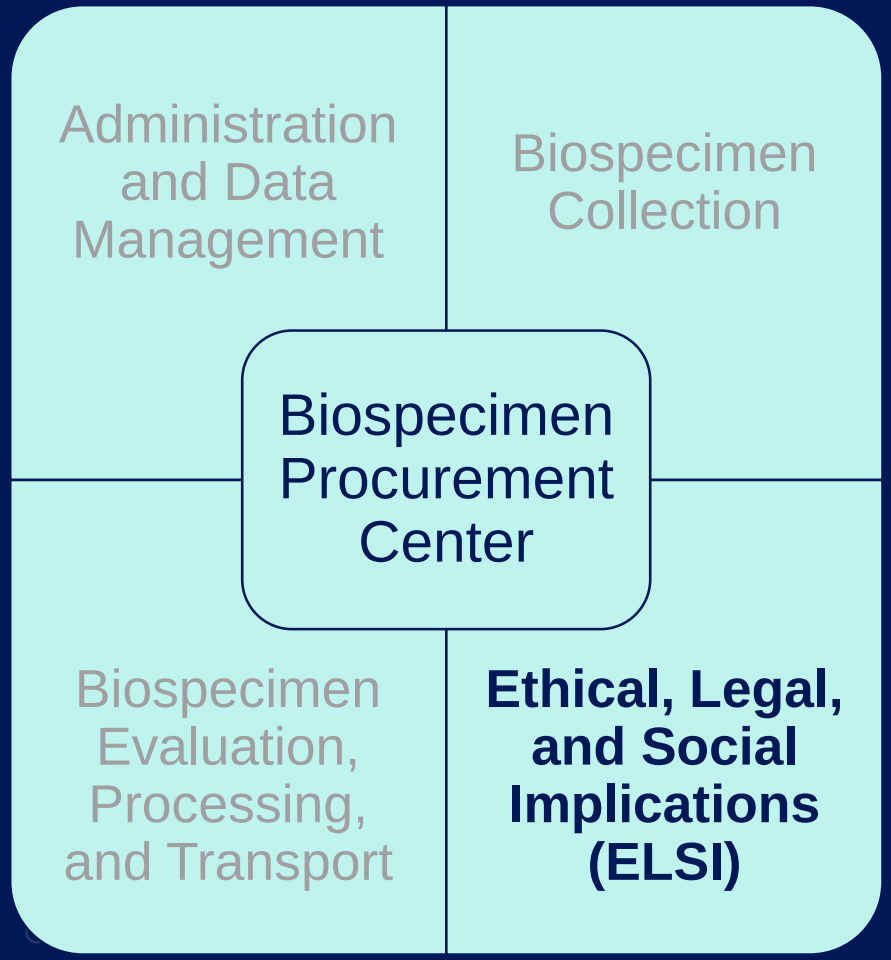
Biospecimen Procurement Center



Ethical, Legal, Social Implications

- Attitudes and concerns of study participants (next of kin)
- Effectiveness of consent process
- Psychosocial impact of participation in study on families and healthcare staff

BPC Research Strategy

Project Overview

- Overall organizational structure and details of each component
- Experience in biospecimen procurement from post-mortem donors
- Plan for coordinating with LDACC
- Summarize collective team expertise and organizational strengths

BPC Research Strategy

Administration and Data Management

- Outline administrative structure
- Procedure for quality control
- Sample workflow management plan
- Policy for managing records
- Establish informatics system for sample tracking and data collection

BPC Research Strategy

Biospecimen Collection, Evaluation, Processing and Transport

- Coordination of expert clinical and technical personnel to acquire post-mortem tissues resulting in high-quality nucleic acids (DNA and RNA) and pathological evaluation
- Clinical data collection
- Suitable storage and shipment of obtained tissues, and transfer of associated clinical data

BPC Research Strategy

Ethical, Legal, and Social Implications

- Management plan how ELSI research will be integrated with tissue collection
- Strategy to approach families for consent and follow-up of research results
- Plans to identify and engage relevant communities and stakeholders

BPC Review Criteria

Scored Review Criteria

- Significance
  - Will the completion of the project result in a useful resource for the research community to drive the field forward?
- Investigator(s)
  - Are the PD(s)/PI(s), collaborators, and other researchers well suited for the project in terms of expertise and effort?
- Innovation
  - Are novel strategies employed to ensure success of the project?
- Approach
  - Is the conceptual design and overall operating plan adequate to procure and preserve tissue samples across developmental stages?
- Environment
  - Are the institutional support, equipment and other physical resources available for the successful completion of the project?

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Laboratory, Data Analysis, Coordinating Center Award

Award

- One award
- Cooperative agreement U24 mechanism

Budget

- Total cost $14.25M over the five-year budget
- $1.5M - $3.5M Total cost
- In addition - $1.6M Total cost per year for brain sequencing and single cell analysis

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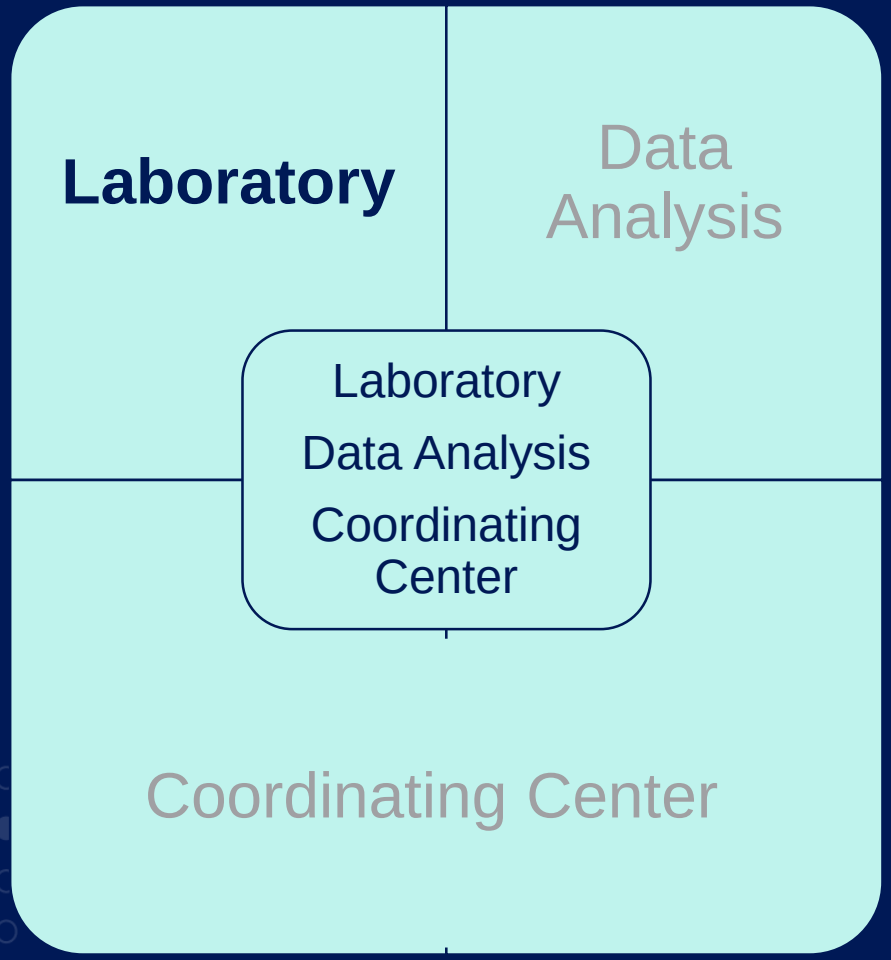
Laboratory, Data Analysis, Coordinating Center



Laboratory

- Receive tissue aliquots from BPC
- Purify nucleic acids (DNA, RNA)
- Perform whole genome sequencing on blood, transcriptome sequencing on subset of bulk tissues and single-cell populations
- Biobanking for preservation of tissue aliquots

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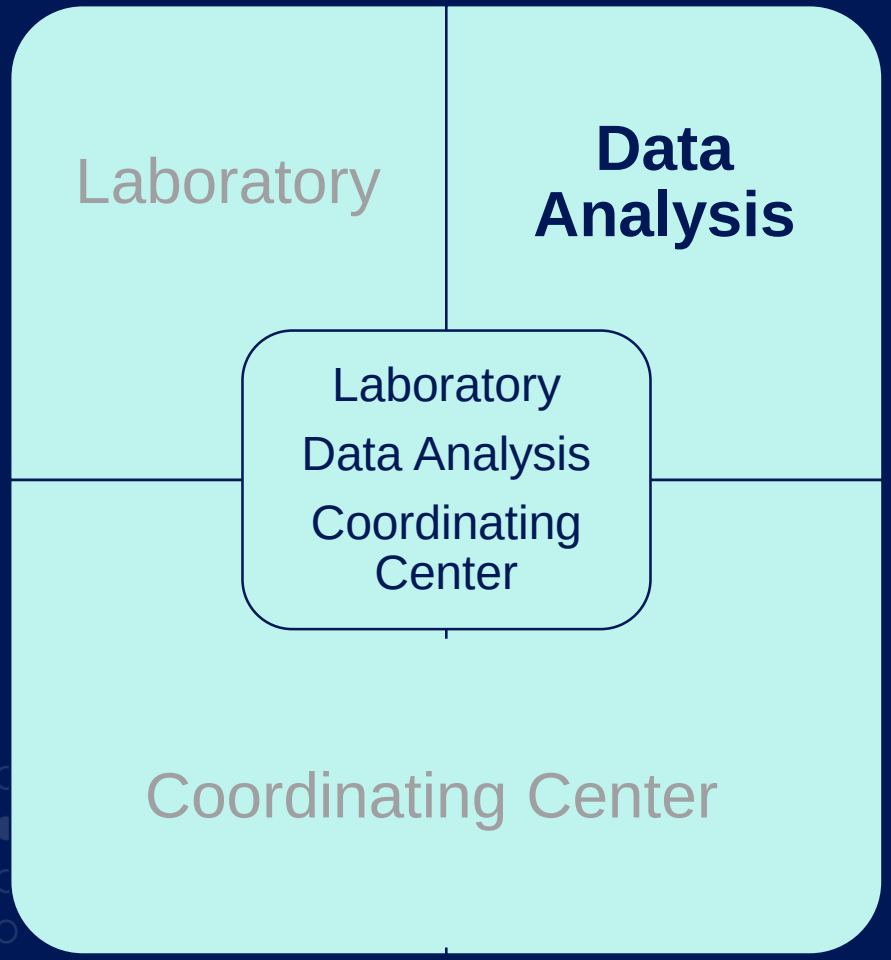
Laboratory, Data Analysis, Coordinating Center



Data Analysis and Management

- Basic analyses
  - Genotyping and gene expression analysis at tissue and single-cell level
- Prepare datasets for public data release (AnVIL)
  - QA/QC
  - Harmonize metadata
  - Facilitate integration with GTEx data

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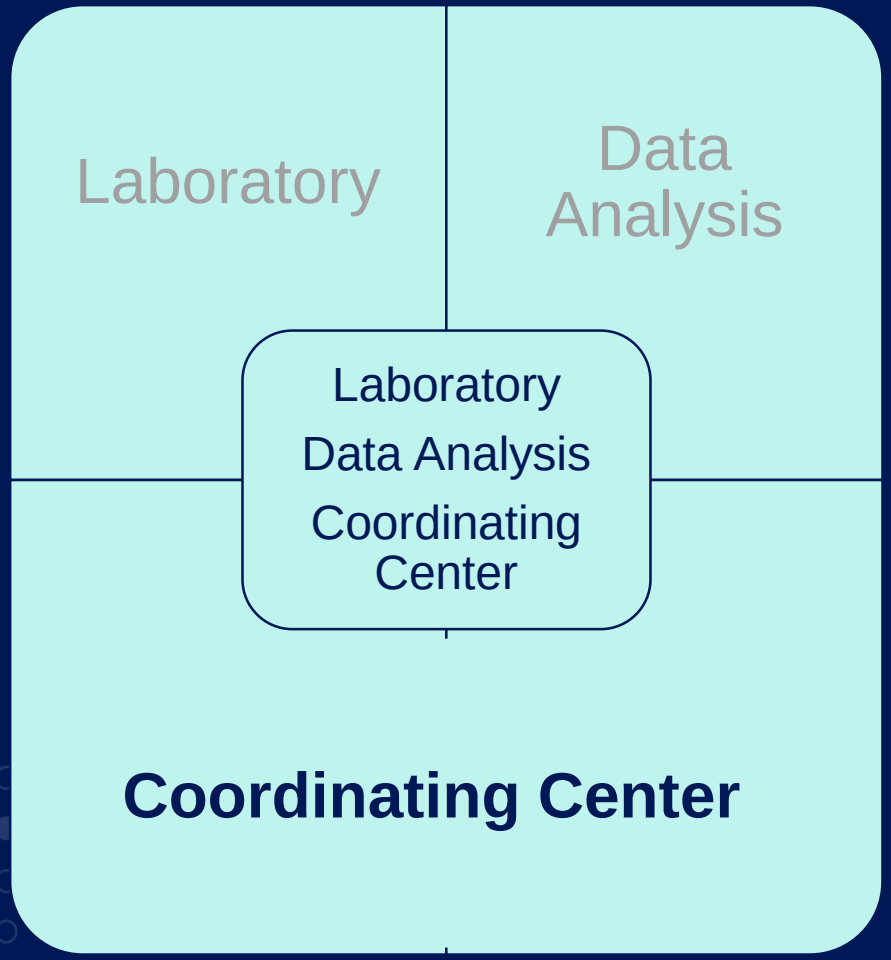
Laboratory, Data Analysis, Coordinating Center



Coordinating Center

- Monitor study progress and lab performance
- Prepare general research reports
- Work with BPC to standardize data collection forms → link clinical and family information to tissue samples
- Manage project logistics
  - Organize working group calls
  - Organize 2 in-person SC meetings/yr and one remote SC meeting
  - Provide travel for ESP to attend SC meetings

LDACC Research Strategy

Laboratory

- Develop protocols for high quality nucleic acids (DNA, RNA) for bulk tissue and single cell sequencing
  - Characterization of brain tissue
- Plan for preservation of tissue aliquots for further analyses
- Plan for genome (blood) and transcriptome sequencing (subset of tissues)
- Plan for single cell assays
- Plan to provide aliquots to research community

LDACC Research Strategy

Data Analysis and Management

- Plan to prepare datasets for public release
- Develop plans for genotyping and gene expression
- Compare and integrate with original GTEx dataset
- Single cell analysis – contain meta data standards regarding technology, QC, cell location registration etc.

LDACC Research Strategy

Coordinating Center

- Monitor study progress, laboratory performance, preparation of statistical and other reports
- In coordination with BPC
  - Barcode-based identification with donor information
  - Report measures number of donors and tissues
  - Standardize data collection forms

LDACC Review Criteria

Scored Review Criteria

- Significance
  - Assess how proposed dGTEx data are interoperable with GTEx data?
- Investigator(s)
  - Will PD(s)/PI(s) dedicate sufficient time to meet needs of project?
- Innovation
  - Are data plans sufficiently innovative to meet the goals of the project?
- Approach
  - Will conceptual design and overall operating plan effectively investigate gene expression across developmental stages?
  - Is the approach to single cell sequencing and analysis robust?
- Environment

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Timeline

Year 1

Development of protocols

BPC – assemble teams for procurement; ELSI research; set up CAB
LDACC – set up infrastructure to receive tissue samples
NIH – set up ESP

Years 2 - 4

Ramp up – tissue procurement, sequencing, ELSI research

BPC – recruit 120 donors; pathology review; send samples to LDACC
LDACC – WGS on blood, transcriptome seq on selected bulk tissues and single cells; gene expression analysis; deposit data in AnVIL; monitor study progress

Year 5

Ramp down

BPC – remaining recruitment
LDACC – sequencing and analysis
Publications, lessons learned

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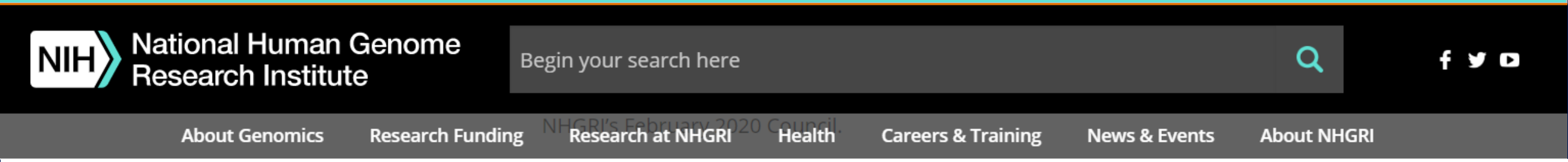
Resources



NHGRI's February 2020 Council

Funding Opportunities

Pediatric Biospecimen Procurement Center (BPC) Supporting the Developmental Gene Expression (dGTEx) Project (U24 Clinical Trial Not Allowed)
RFA-HD-21-008
Application Due Date(s): December 3, 2020
Expiration Date: December 4, 2020

Laboratory, Data Analysis, and Coordinating Center (LDACC) for the Developmental Genotype-Tissue Expression Project (U24 Clinical Trial Not Allowed)
RFA-HG-20-039
Application Due Date(s): November 13, 2020
Expiration Date: November 14, 2020

URL: https://www.genome.gov/Funded-Programs-Projects/Developmental-Genotype-Tissue-Expression

RFA Key Dates

- Laboratory, Data Analysis, Coordinating Center RFA (HG-20-039)
  - Letters of Intent due October 13, 2020
  - Applications due November 13, 2020
  - Award – June 2021
- Biospecimen Procurement Center RFA (HD-20-008)
  - Letters of Intent due November 3, 2020
  - Applications due December 3, 2020
  - Award – June 2021

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FAQs

- Is the Letter of Intent mandatory? No, this is optional
- Is this an open competition? Yes, anyone can apply
- How will LDACC work with AnVIL? - Data on gene expression and data analysis should be deposited in AnVIL on a timely and regular basis.
- Will there be RFAs for data analysis? FOAs likely in later years.
- Is ELSI study required? Yes

Acknowledgements

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Melissa Parisi
Zhaoxia Ren
Jen Troyer
Simona Volpi

Applicant Q&A

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