CCSS Biorepository

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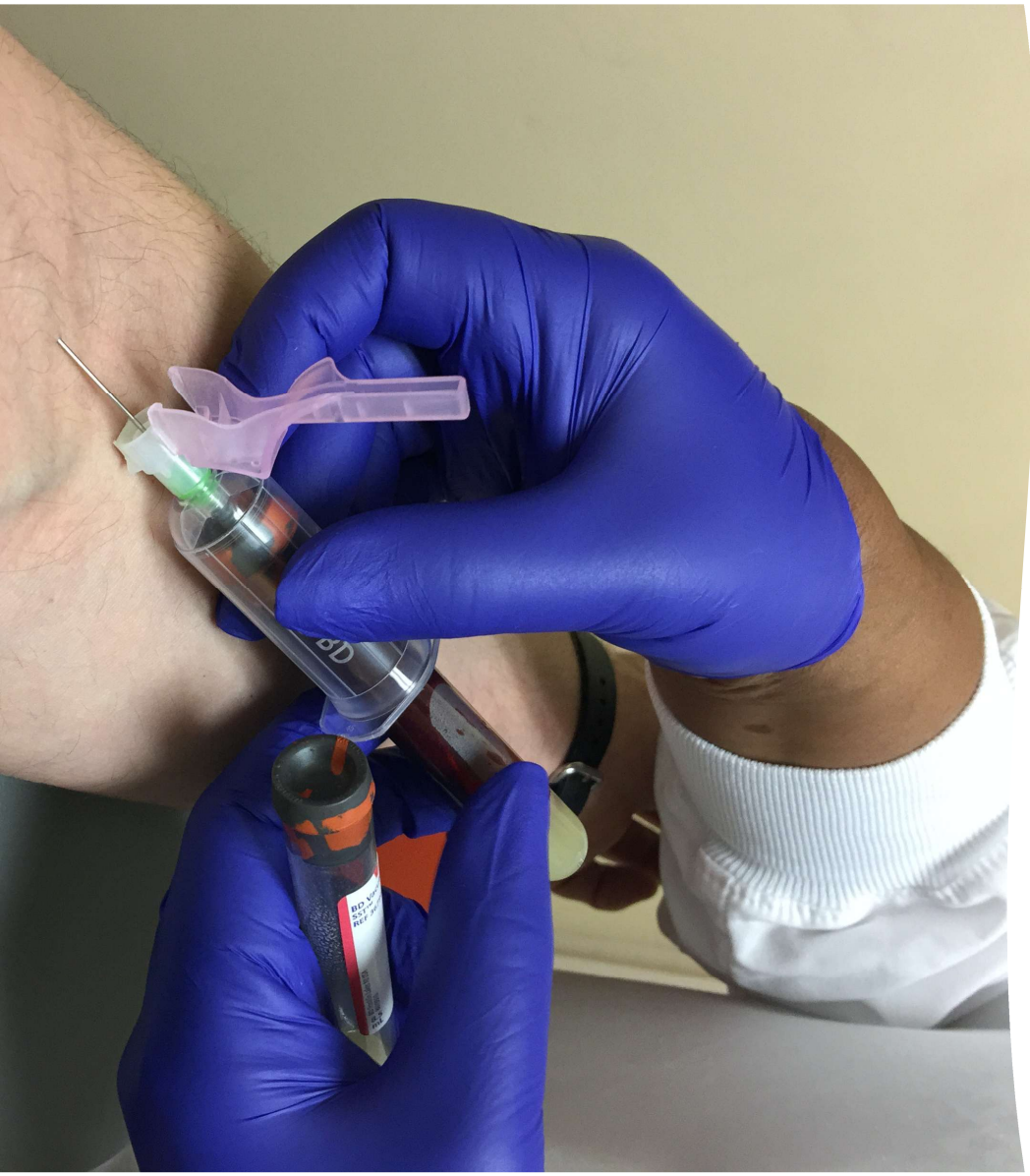
Why ~~Do~~ Should I Care About Biospecimens?

- Biology paired with clinical and epidemiological observations makes for a great paper!
- Reviewers like an added biological question
- Biology is fun!
- If this is not your thing, there is plenty of help within CCSS to discuss what might (or might not) be possible- call people-it can't hurt!



Blood Samples: specific clinical phenotypes and specific studies

- Subsequent malignant neoplasms
- Interventional or observational studies with direct patient contact and necessary funding

What Can I Do With Plasma Samples?

- Proteomics
  - Agnostic- can discover totally unknown associations
  - Expensive
  - Needs validation

- Candidate biomarker studies with ELISA etc
  - Need candidate genes
  - Less expensive
  - Quicker

Diagnosis	Total Number of Plasma Samples
ALL	1423
AML	1211
Other Leukemia	158
Astrocytoma	290
Medulloblastoma/PNET	175
Other CNS tumor	88
Hodgkin Lymphoma	682
NHL	343
Kidney tumor	317
Neuroblastoma	215
Soft Tissue Sarcoma	297
Ewing Sarcoma of Bone	148
Osteosarcoma	301
Other Bone Tumor	18
TOTAL	**4298**

What Can I Do With Peripheral Blood Mononuclear Cells?

- Blood samples have been layered over Ficoll and centrifuged to separate out peripheral blood mononuclear cells (lymphocytes, monocytes).
- Cells are frozen as viable cells at minus 80^{o}C in freeze medium.
- Cells can be thawed and studied, thawed and cultured for a short time and thawed and used as a source of nucleic acids or intracellular proteins.

Diagnosis	Total Number of PBMC Samples
ALL	1218
AML	161
Other Leukemia	56
Astrocytoma	291
Medulloblastoma/PNET	172
Other CNS tumor	88
Hodgkin Lymphoma	696
NHL	339
Kidney tumor	314
Neuroblastoma	217
Soft Tissue Sarcoma	299
Ewing Sarcoma of Bone	151
Osteosarcoma	300
Other Bone Tumor	17
TOTAL	**4319**

Available Whole Exome/Genome Data

BAM files and phenotype data available to all investigators through completion of a Data Access Procedures process in the St. Jude Cloud.

Public Access Whole Genome Data Tables

The table below provides characteristics for genome sequenced CCSS participants.

Characteristic	CCSS Participants with Whole Exome Data (N=2641)	
	N	%
Sex		
Male	1240	47.5
Female	1401	52.5
Ancestry (based on genotype)		
European	2114	78.8
Non-European	527	21.2

Using whole exome/genome data for discovery or validation

Gene-Level Analysis of Anthracycline-Induced Cardiomyopathy in Cancer Survivors

A Report From COG-ALTE03N1, BMTSS, and CCSS

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ABSTRACT

BACKGROUND Anthracyclines are highly effective in treating cancer, albeit with increased cardiomyopathy risk. Although risk is attributed to associations with single nucleotide polymorphisms (SNPs), multiple SNPs on a gene and their interactions remain unexamined.

OBJECTIVES This study examined gene-level associations with cardiomyopathy among cancer survivors using whole-exome sequencing data.

METHODS For discovery, 278 childhood cancer survivors (129 cases; 149 matched control subjects) from the COG (Children's Oncology Group) study ALTE03N1 were included. Logic regression (machine learning) was used to identify gene-level SNP combinations for 7,212 genes and ordinal logistic regression to estimate gene-level associations with cardiomyopathy. Models were adjusted for primary cancer, age at cancer diagnosis, sex, race/ethnicity, cumulative anthracycline dose, chest radiation, cardiovascular risk factors, and 3 principal components. Statistical significance threshold of 6.93×10^{-6} accounted for multiple testing. Three independent cancer survivor populations (COG study, BMTSS [Blood or Marrow Transplant Survivor Study] and CCSS [Childhood Cancer Survivor Study]) were used to replicate gene-level associations and examine SNP-level associations from discovery genes using ordinal logistic, conditional logistic, and Cox regression models, respectively.

Original Reports | Pediatric Oncology

Polygenic Risk and Chemotherapy-Related Subsequent Malignancies in Childhood Cancer Survivors: A Childhood Cancer Survivor Study and St Jude Lifetime Cohort Study Report

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ABSTRACT

PURPOSE Chemotherapeutic exposures are associated with subsequent malignant neoplasm (SMN) risk. The role of genetic susceptibility in chemotherapy-related SMNs should be defined as use of radiation therapy (RT) decreases.

PATIENTS AND METHODS SMNs among long-term childhood cancer survivors of European (EUR; N = 9,895) and African (AFR; N = 718) genetic ancestry from the Childhood Cancer Survivor Study and St Jude Lifetime Cohort Study were evaluated. An externally validated 179-variant polygenic risk score (PRS) associated with pleiotropic adult cancer risk from the UK Biobank Study (N > 400,000) was computed for each survivor. SMN cumulative incidence comparing top and bottom PRS quintiles was estimated, along with hazard ratios (HRs) from proportional hazards models.

ACCOMPANYING CONTENT

Data Supplement

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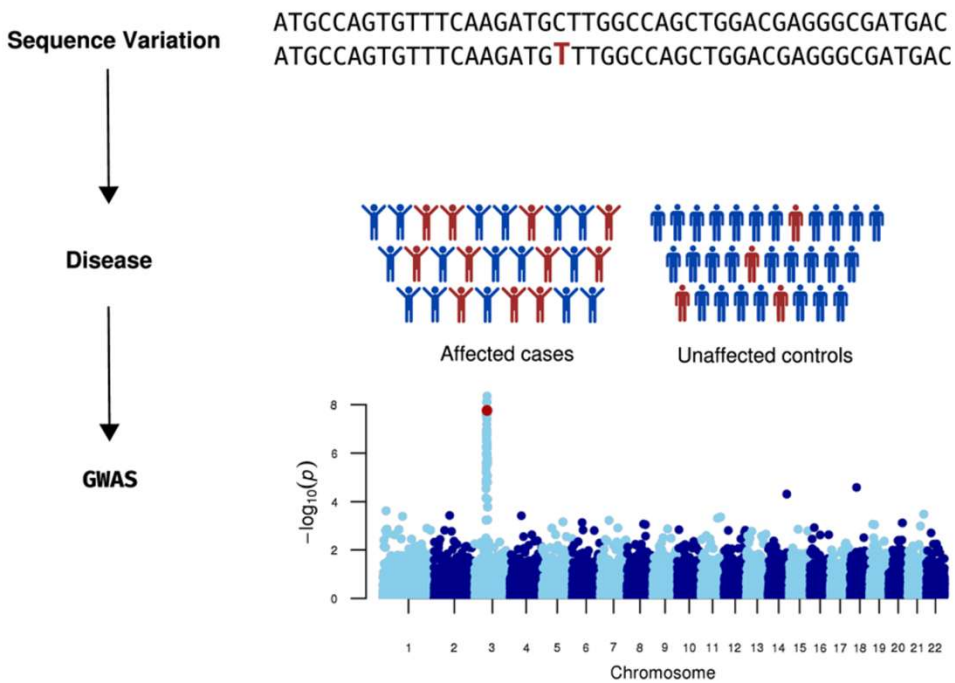
Saliva Collection

In December 2007, collection of a saliva sample using the Genotek Oragene-DNA Self-Collection Kit was initiated. Oragene-DNA yields high-quality, high-quantity (@ 110ug) DNA from a small saliva sample. Oragene-DNA is optimized to preserve and stabilize saliva samples for long term storage at room temperature without DNA degradation. DNA from Oragene-DNA is equivalent to DNA from blood and has been successfully used for PCR and genotyping in genome-wide Association studies.

GWAS Data Resource



The Childhood Cancer Survivor Study genome-wide association study (GWAS) dataset is available to investigate the role of genetic susceptibility in the development of non-malignant treatment-related outcomes (in addition to subsequent malignancies) in cancer survivors. This process is open to investigators through collaboration with CCSS and National Cancer Institute investigators in the use of existing GWAS data and corresponding outcomes-related data to address innovative research questions relating to potential genetic contributions to risk for treatment-related outcomes through submission of an Application of Intent. The links below will guide you in submitting a proposal.

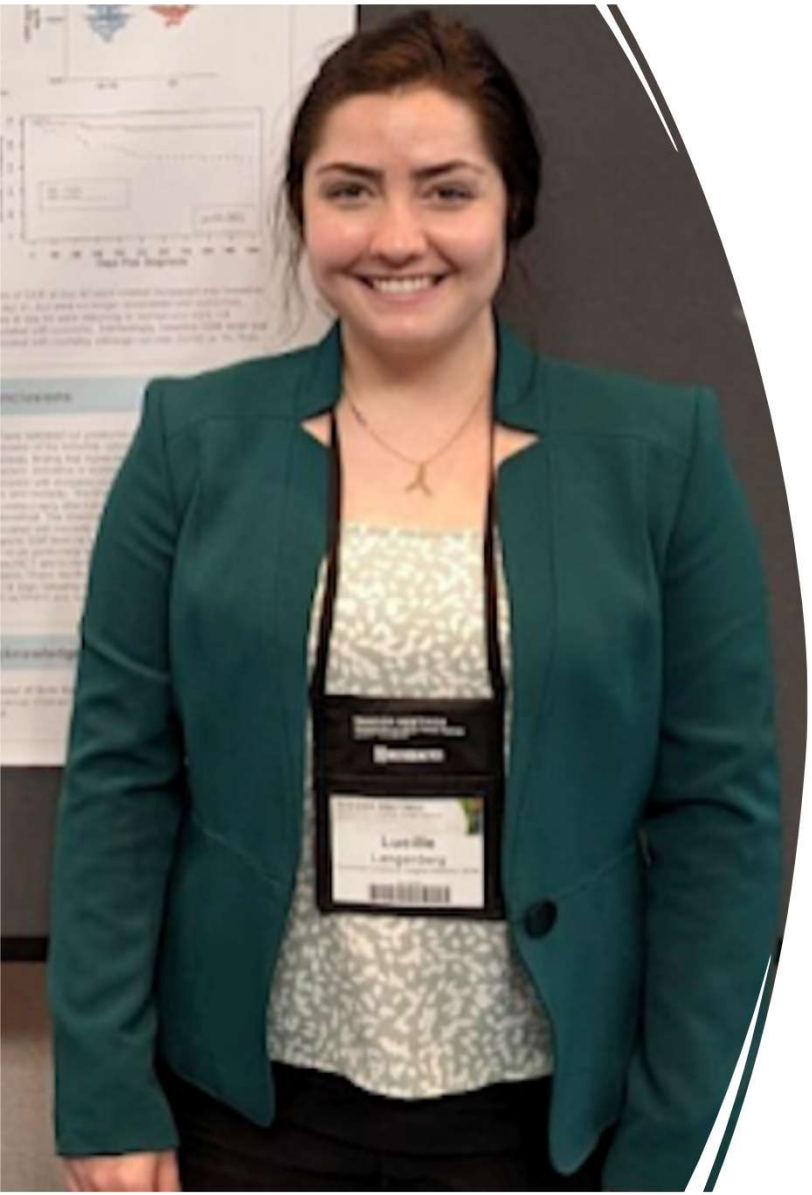
What Can I Do With Saliva Samples?

- Samples provide DNA only, no RNA and no protein
- Small amounts of DNA and lower quality than DNA from blood
- Most suitable for studies of candidate genes, eg SNP's
- Check first if there are data already in GWAS/sequencing repository

Diagnosis	Total Number of Oragene Samples
ALL	2614
AML	363
Other Leukemia	115
Astrocytoma	954
Medulloblastoma/PNET	417
Other CNS tumor	264
Hodgkin Lymphoma	1291
NHL	813
Kidney tumor	927
Neuroblastoma	699
Soft Tissue Sarcoma	654
Ewing Sarcoma of Bone	278
Osteosarcoma	462
Other Bone Tumor	40
Sibling Controls	**1635**
TOTAL	**11,526**

Biorepository Summary

- Samples are a gracious gift from our participants and are an invaluable resource and can strengthen almost any grant application
- CCSS will be very happy if all the samples get used!
- Data are forever- resources like the GWAS and genome sequencing dataset are available, already paid for and can also greatly enhance a project
- If you have questions I can help you with, please contact me: **Stella.Davies@cchmc.org**



Lucy Langenberg, BS