GLOBAL
DOWN SYNDROME
FOUNDATION®

Down
Syndrome
Alliance
OF THE MIDLANDS

LINDA CRNIC
INSTITUTE
FOR DOWN SYNDROME™

HumanTrisomeProject

Leah Janke, Executive Director
DSA of the Midlands

Keith Smith
Keith.Smith@ucdenver.edu

The Inspiration

Anna and John J. Sie

Sophia Kay Whitten and her brother, Patrick

"Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has."
Margaret Mead

Our Unique Affiliate Model!

The Global Down Syndrome Foundation is part of a network of affiliate organizations that work closely together on a daily basis to deliver on our mission, vision, values, and goals:

Global & Affiliates

GLOBAL DOWN SYNDROME FOUNDATION
- Fundraising & Development
- Outreach, Advocacy & Education

CRNIC INSTITUTE FOR DOWN SYNDROME
- Basic Research
- Clinical Research

SIE CENTER FOR DOWN SYNDROME
- Pediatric Medical Care
- Clinical Research

ROCKY MOUNTAIN ALZHEIMER'S DISEASE CENTER
- Medical Care
- Basic & Clinical Research

Coming Soon:
ADULT CLINIC
- Adult Medical Care
- Clinical Research

❖**Global:** was established as a 501(c)3 in 2009 and is "Dedicated to significantly improving the lives of people with Down syndrome through Research, Medical Care, Education, and Advocacy"

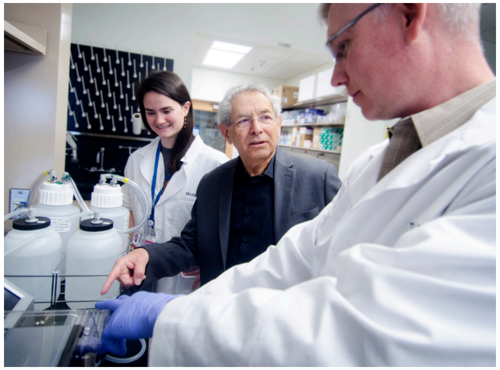
❖**Affiliates are:**
- ➢Established with a lead gift from Anna & John J. Sie Foundation
- ➢Must work closely together to benefit people with Down syndrome
- ➢Must be self-sustaining financially

Crnic Institute for Down Syndrome

The First
Academic Home for Down Syndrome Research & Medical Care

Crnic Institute is the 1st Academic Home for DS Research & Medical Care

- **38 Labs & Over 120 scientists working on DS research through the Crnic Institute**
  - 93 Super Group members – Large monthly meetings
  - SAB includes Nobel Laureate Dr. Tom Cech, and renowned scientists such as Drs. Larry Gold, Angelika Amon and Jeanne Lawrence
- **Global Core competencies – DS and Alzheimer's Disease, DS and Cancer, DS and Autoimmune Diseases**
  - Other competencies – Autism, Cognition, Biology, Genetics and more
- **Creating a Pipeline of Scientists**
  - Scholarships for Graduate Students, Post-docs, and Fellows in DS Research that are now supported by two long-term funds



Crnic Institute Mission & Vision

- Significantly improve the lives of all people with Down syndrome
- Change the paradigm of how people with Down syndrome are perceived by society
- Change the paradigm of how people with Down syndrome are served in research and the medical care community
- Contribute meaningfully to something near and dear to our hearts

Delivering on our Mission & Vision

→ We have Global representing self advocates and families at the table ensuring the priorities of the science benefit people with Down syndrome

→ We have a team of scientists not only first in class but mission driven to make a difference (best minds & best hearts!)

→ We have brought together scientists and clinicians

→ We have an A+ Community of Down syndrome organizations who understand the importance of goal driven research

→ NIH and key scientist understand the importance.

Crnic Institute Human Trisome Project^{TM} Biobank: A platform for transformational research

Crnic Institute Human Trisome Project (HTP)

- A clinical research study using the most advanced technology to understand what diseases and conditions people with Trisomy 21 are protected from and predisposed to
- The largest, most detailed study of people with Trisomy 21
- To create the largest public database for Down syndrome research to date
- To create the most comprehensive biobank of biological samples for Down syndrome research

Project goals

1. To enable a Precision Medicine approach to Down syndrome.
2. To define how trisomy 21 causes a novel disease spectrum.
3. To develop novel diagnostic and therapeutic tools that will benefit those with trisomy 21, and also millions of typical individuals.

People with Down syndrome have a different ‘disease spectrum’

Heart Disease

Cancer

Stroke

Alzheimer’s

Diabetes

Altogether, these 5 conditions account for ~58% of deaths in the U.S.A.

People with Down syndrome have a different ‘disease spectrum’

An extra copy of ~200 genes modulates most major medical conditions!

Heart Disease

Cancer

Coronary Artery Disease
Atherosclerosis
Hypertension
Angiopathies

Alzheimer’s

Diabetes

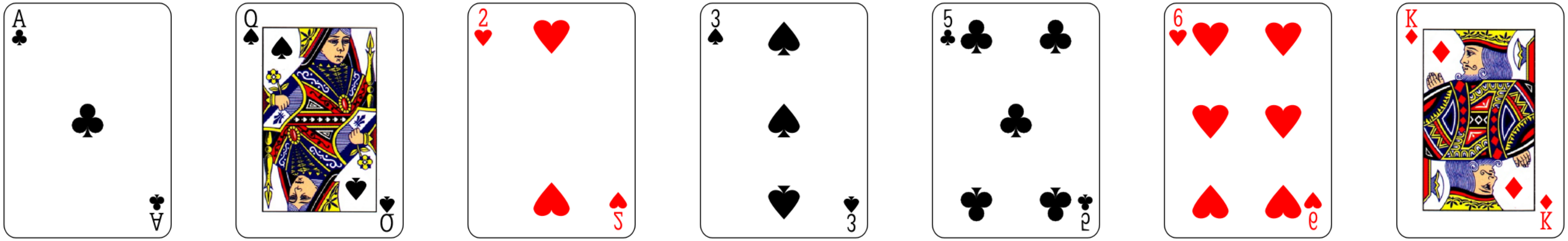
Autism
Congenital Heart Defects
Celiac Disease
Thyroid Dysfunction
Autoimmune Disorders
Vision Problems
Hearing Problems
Intestinal Atresia
Sleep Apnea

The ~6 million human beings alive today with trisomy 21 may hold solutions to many major medical conditions

The thinking behind the HTP
"A black box"

Trisomy 21

Down syndrome



Celiac Disease	Intestinal Atresias	Thyroid Dysfunction	Seizures	Leukemia	Congenital Heart Defects	Autism
~5%	~12%	up to 18%	up to 13%	~1%	40-50%	up to 10%

Each person is dealing with Trisomy 21 in his/her own unique, personal way

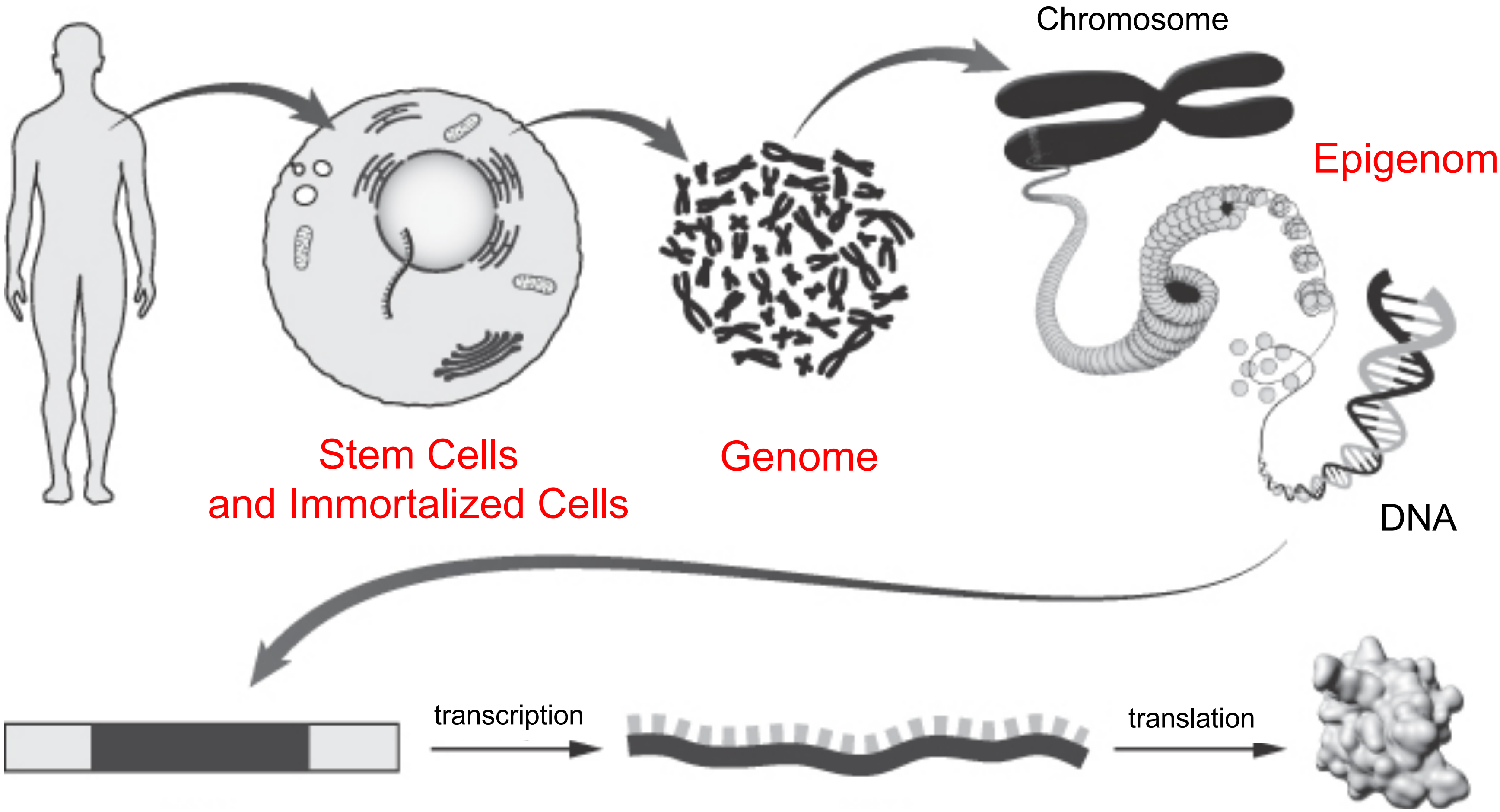
They are more awesome than different,
yet they are **ALL** different

Our motto:

Nothing in the study of Down syndrome makes sense except in the light of Personalized Medicine

Opening the Black Box: The Ten Layers

Digital Phenotypes



Epigenome

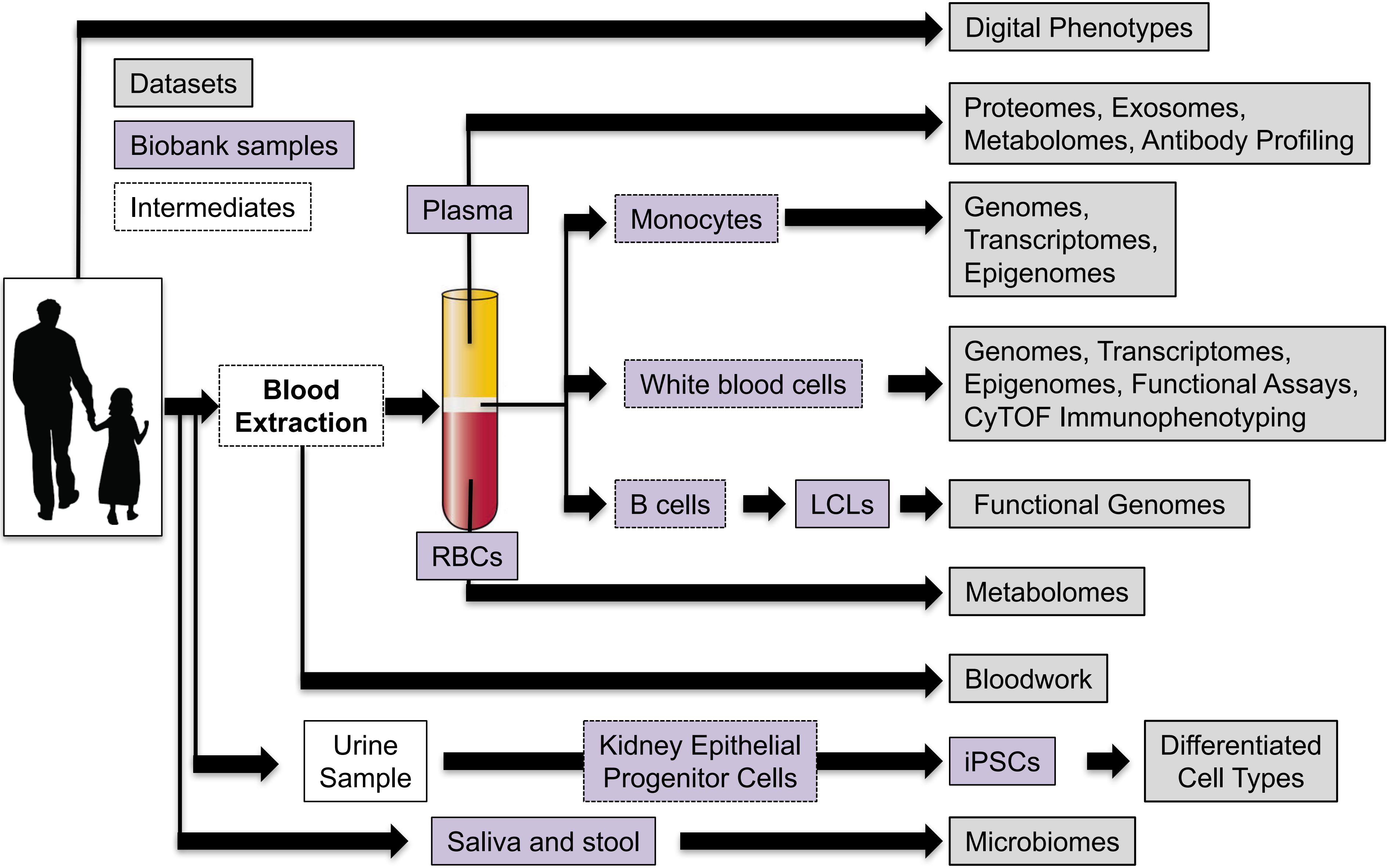
Stem Cells
and Immortalized Cells

Genome

Transcriptome

Proteome

A large cohort study with multi-omics datasets, deep clinical data and a matching multi-dimensional biobank



Digital Phenotypes

Datasets

Biobank samples

Intermediates

Proteomes, Exosomes, Metabolomes, Antibody Profiling

Plasma

Monocytes

Genomes, Transcriptomes, Epigenomes

Blood Extraction

White blood cells

Genomes, Transcriptomes, Epigenomes, Functional Assays, CyTOF Immunophenotyping

B cells

LCLs

Functional Genomes

RBCs

Metabolomes

Bloodwork

Urine Sample

Kidney Epithelial Progenitor Cells

iPSCs

Differentiated Cell Types

Saliva and stool

Microbiomes

LCLs: lymphoblast cell lines, iPSCs: induced pluripotent stem cells, RBCs: red blood cells

A team of clinical researchers gathers clinical data

Digital Phenotypes

The Sie Center and Rocky Mountain Alzheimer's Disease Center (and soon the Denver Adult Clinic) administer rich databases with hundreds of clinical metadata fields

Fran Hickey

Children's Hospital Colorado
Anna and John J. Sie Center for Down Syndrome

Hunt Potter

Rocky Mountain Alzheimer's Disease Center
SCHOOL OF MEDICINE | UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Barry Martin

Denver Adult Clinic
(coming soon)

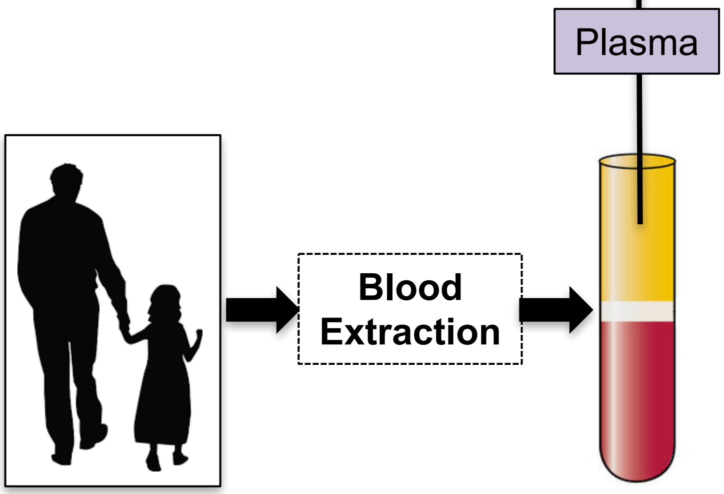
Clinical researchers in the Human Trisome Project team annotate medical records and online participant surveys to create a rich REDcap database for each participant

Angela Rachubinski

Erich Butcher

Juana Marmolejo

Plasma samples are stored for generation of proteomics data, neuronal and glial exosome analysis, metabolomics data and antibody profiling



Blood Extraction

Plasma

Proteomes, Exosomes, Metabolomes, Antibody Profiling

Plasma Proteomics **Inflammatory Markers**

Tom Blumenthal

Donald Evans

Keith Smith

Exosome Analysis

Hunt Potter

Brianne Bettcher

Metabolomics

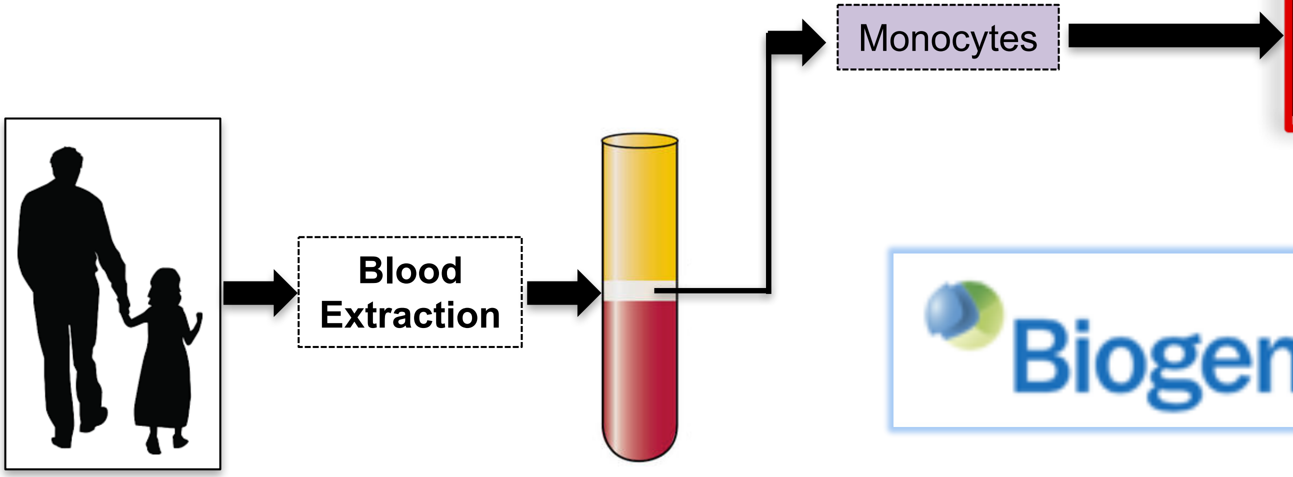
Rani Powers

Angelo D'Alessandro

Antibody Profiling

Stephanie James

Monocytes are purified and shipped to Biogen for generation of diverse datasets through a sponsored research agreement



Blood Extraction

Monocytes

Genomes,
Transcriptomes,
Epigenomes

Biogen

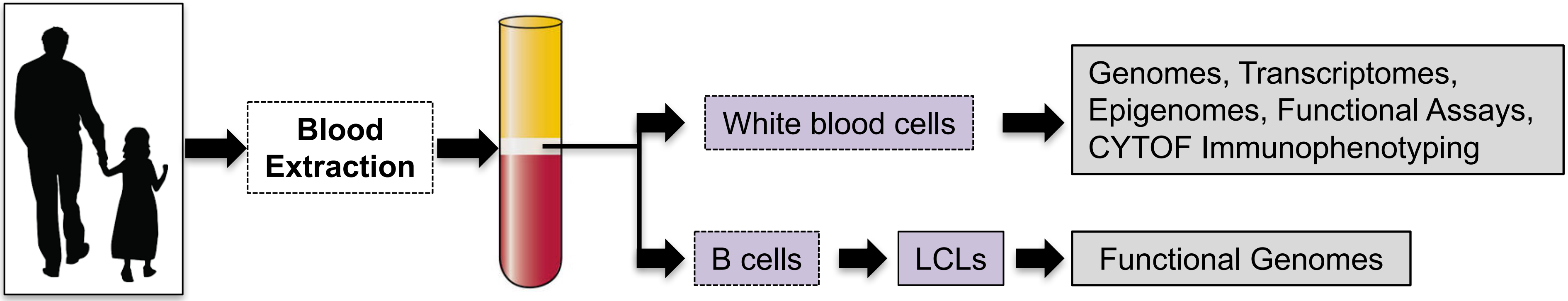
Donald Evans

Biogen generates SNP data, DNA methylome analysis, RNA-seq data and ATAC-seq chromatin accessibility data.

Since monocytes are key players in neuroinflammation during Alzheimer’s disease progression, these analyses could provide early biomarkers and novel mechanistic insights.

The sample processing team purifies CD4+ T cells, CD8+ T cells, T regs, B cells, monocytes and Natural Killers for generation of diverse –omics datasets, functional assays and lymphoblastoid cell lines

Every sample is analyzed by CyTOF for characterization of 150+ immune cell subtypes



Blood Extraction

White blood cells

Genomes, Transcriptomes, Epigenomes, Functional Assays, CYTOF Immunophenotyping

B cells

LCLs

Functional Genomes

Transcriptome and Epigenome

CyTOF Immune Phenotyping

Functional Assays (e.g. T reg functional assays)

Kelly Sullivan

Brian O’Connor

Kate Waugh

Elena Hsieh

Paula Araya

Stephanie Moon

Roy Parker

Red blood cells (RBCs) are analyzed for metabolic signatures that differ from those in plasma

Bloodwork includes detailed white cell blood count, cellular morphology by cytospin and smear, and key blood analytes

Blood Extraction

RBCs

Metabolomes

Bloodwork

Metabolomics

Rani Powers

Angelo D'Alessandro

Keith Smith

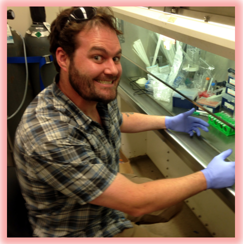
Ross Granrath

Urine samples are processed for purification and amplification of kidney epithelial progenitor cells

In turn, these are used to generate iPSCs with a novel RNA-based, vector-free protocol

iPSCs are then used to generate specific cell types and organoids

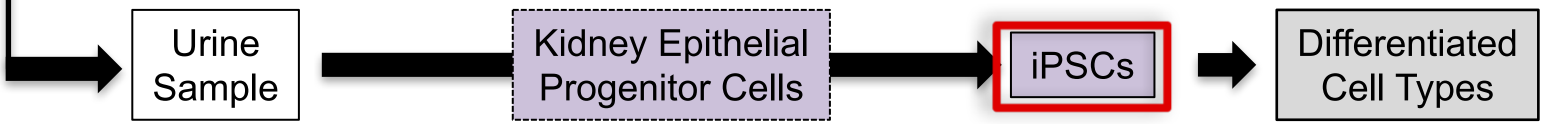
Ganna
Bilousova



Tristan
McLure-Begley

Will
Old

Michael
Klymkowsky



Urine Sample → Kidney Epithelial Progenitor Cells → iPSCs → Differentiated Cell Types

Saliva and stool samples are also collected and stored

These samples are used to define the oral and gut microbiome as well as functional assays

Oral and gut microbiomes

Ken Krauter

Brittany Demmit

Oral candidiasis and saliva antimicrobial activities

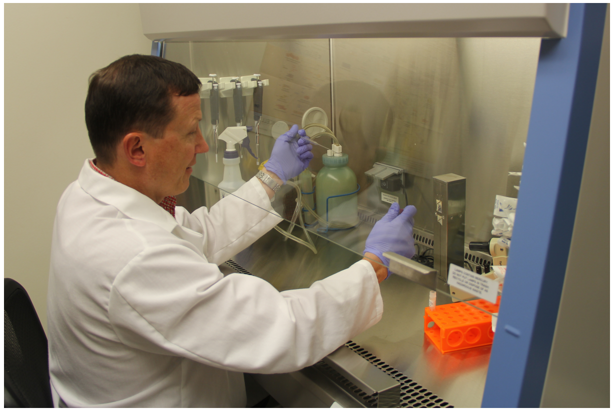
Michalis Lionakis
(NIAID)

Saliva and stool → Microbiomes

An Unprecedented Discovery Engine-Lots of Data

From **1000** individuals with Down syndrome, we will obtain:

genomes
epigenomes
transcriptomes
proteomes
metabolomes
functional genomes
bloodworks
immortalized cell lines
pluripotent stem cell lines
microbiomes
electronic medical records (EMR)

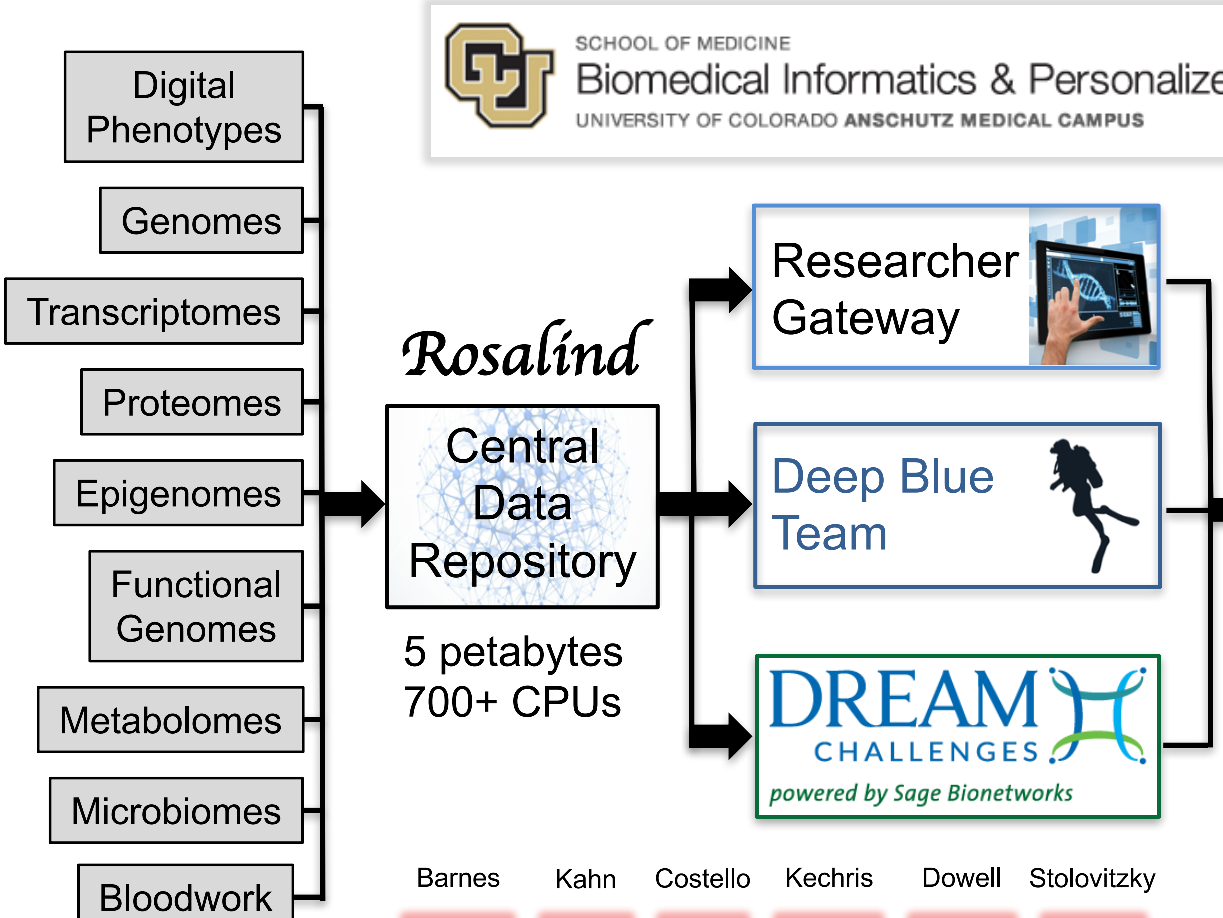


From a single blood draw, with existing technology!

Leave no stone unturned

+ 500 typical controls, 250 of them close relatives

One of the largest datasets ever produced for any medical condition



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- Digital Phenotypes
- Genomes
- Transcriptomes
- Proteomes
- Epigenomes
- Functional Genomes
- Metabolomes
- Microbiomes
- Bloodwork

Rosalind

Central Data Repository

5 petabytes
700+ CPUs

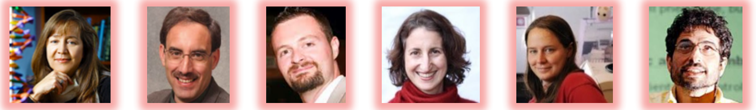
Researcher Gateway

Deep Blue Team

DREAM CHALLENGES
powered by Sage Bionetworks

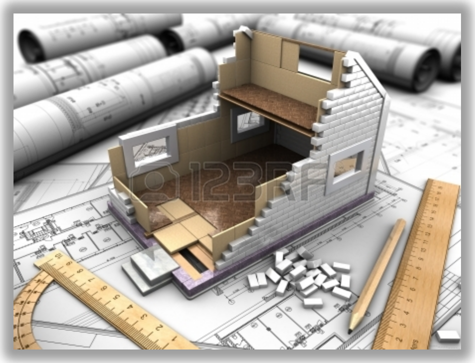
Discoveries!

Barnes Kahn Costello Kechris Dowell Stolovitzky



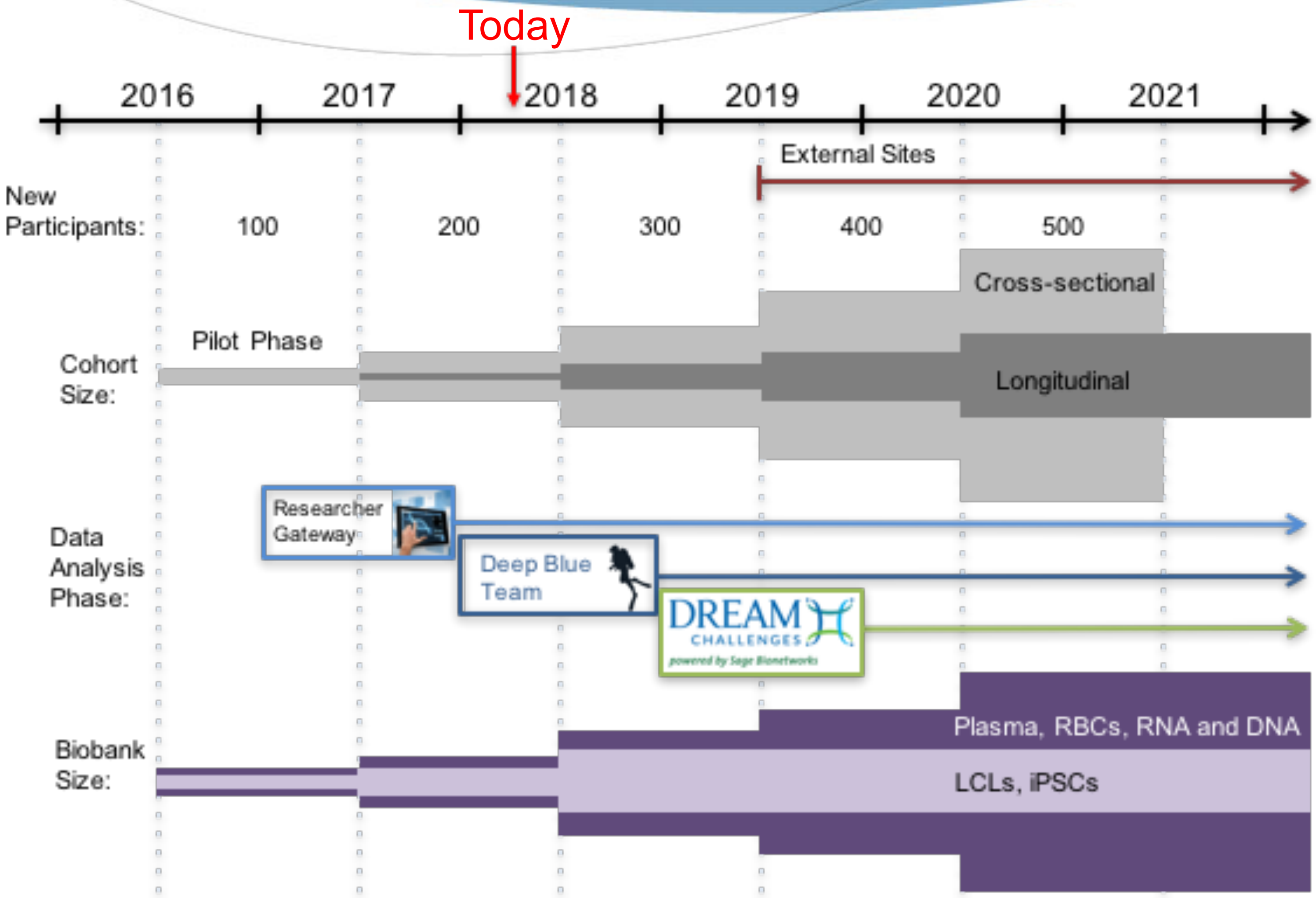
Turning data into discoveries

The Power of
Multidimensional Datasets



Going beyond the blueprint

HTP Timeline – Light Speed for Research…



Original timeline proposed in December 2015

LCLs: lymphoblast cell lines, iPSCs: induced pluripotent stem cells

307 Blood draws to date!

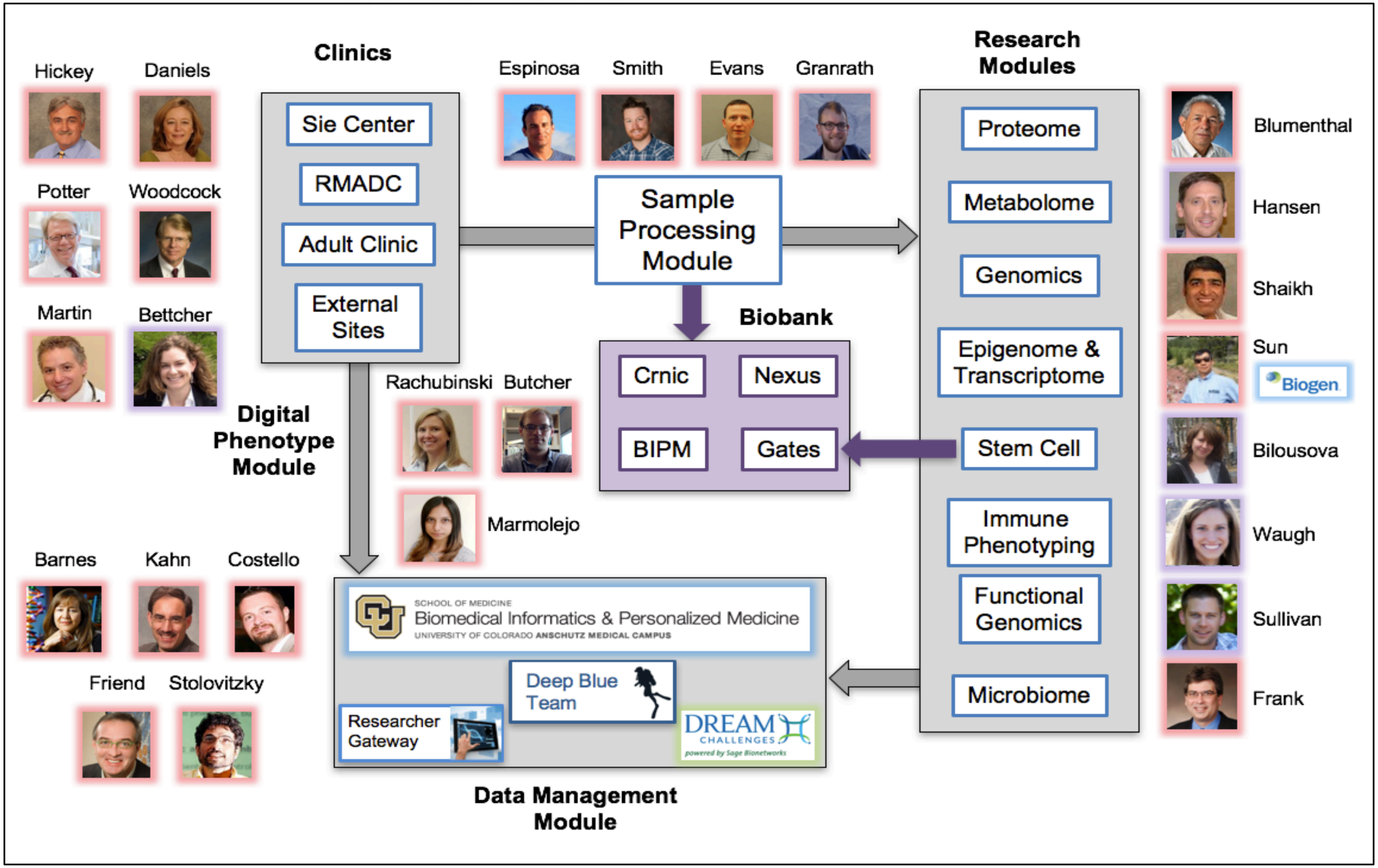
HTP00001

October 10, 2016

HTP00300

September 7, 2017

Blasting into year two of the project!



Hickey
Daniels
Potter
Woodcock
Martin
Bettcher

Clinics

Sie Center
RMADC
Adult Clinic
External Sites

Digital Phenotype Module

Espinosa
Smith
Evans
Granrath

Sample Processing Module

Biobank

Crnic
Nexus
BIPM
Gates

Rachubinski
Butcher
Marmolejo

Research Modules

Proteome
Metabolome
Genomics
Epigenome & Transcriptome
Stem Cell
Immune Phenotyping
Functional Genomics
Microbiome

Blumenthal
Hansen
Shaikh
Sun
Biogen
Bilousova
Waugh
Sullivan
Frank

Barnes
Kahn
Costello
Friend
Stolovitzky

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Deep Blue Team
Researcher Gateway
DREAM CHALLENGES
powered by Sage Bionetworks

Data Management Module

UNLEASHING THE POWER OF THREE!

The Crnic Institute will make the HTP dataset easily accessible and available to the public

- This will raise the entire field of Down syndrome research by providing new scientists with important data/samples/tools
- This will help current scientists who lack a large enough group of participants with Down syndrome to pursue their theories or their dream ideas

The Crnic Institute data collected through the HTP will allow Down syndrome to become the most understood genetic condition versus the least understood

The Crnic Institute data collected through the HTP will help us develop novel diagnostic and therapeutic tools

- First and foremost, benefit those with Trisomy 21, and millions of typical individuals

Trisome.org

LINDA CRNIC INSTITUTE
FOR DOWN SYNDROME™

RESEARCH TO DEVELOP THE HUMAN TRISOME PROJECT BIOBANK

PURPOSE OF THE STUDY

The purpose of this study is to provide qualified and approved researchers with access to biological samples and health information to answer specific research questions. This project will significantly increase the speed of Down syndrome research and the understanding of associated medical conditions such as leukemia and Alzheimer's disease.

WHO CAN PARTICIPATE?

Anyone who is 6 months – 89 years old who:

1. Has Down syndrome (any type, including mosaic or partial Down syndrome/trisomy21)
2. Has a family member with Down syndrome but does not him/herself have Down syndrome
3. Does not have Down syndrome and does not have a family member with Down syndrome (this would be a "control" group to compare with those affected by Down syndrome).

MAIN PROCEDURES INVOLVED

Participation would include a single successful blood draw, a mouth swab and allowing researchers to look at your health information. It is optional to give a stool sample and take part in the study for a longer time frame.

DURATION OF PARTICIPATION

A single visit to collect blood and a mouth swab, fill out a health survey, with the option of a stool sample and repeat visits for a longer term study.

INTERESTED?

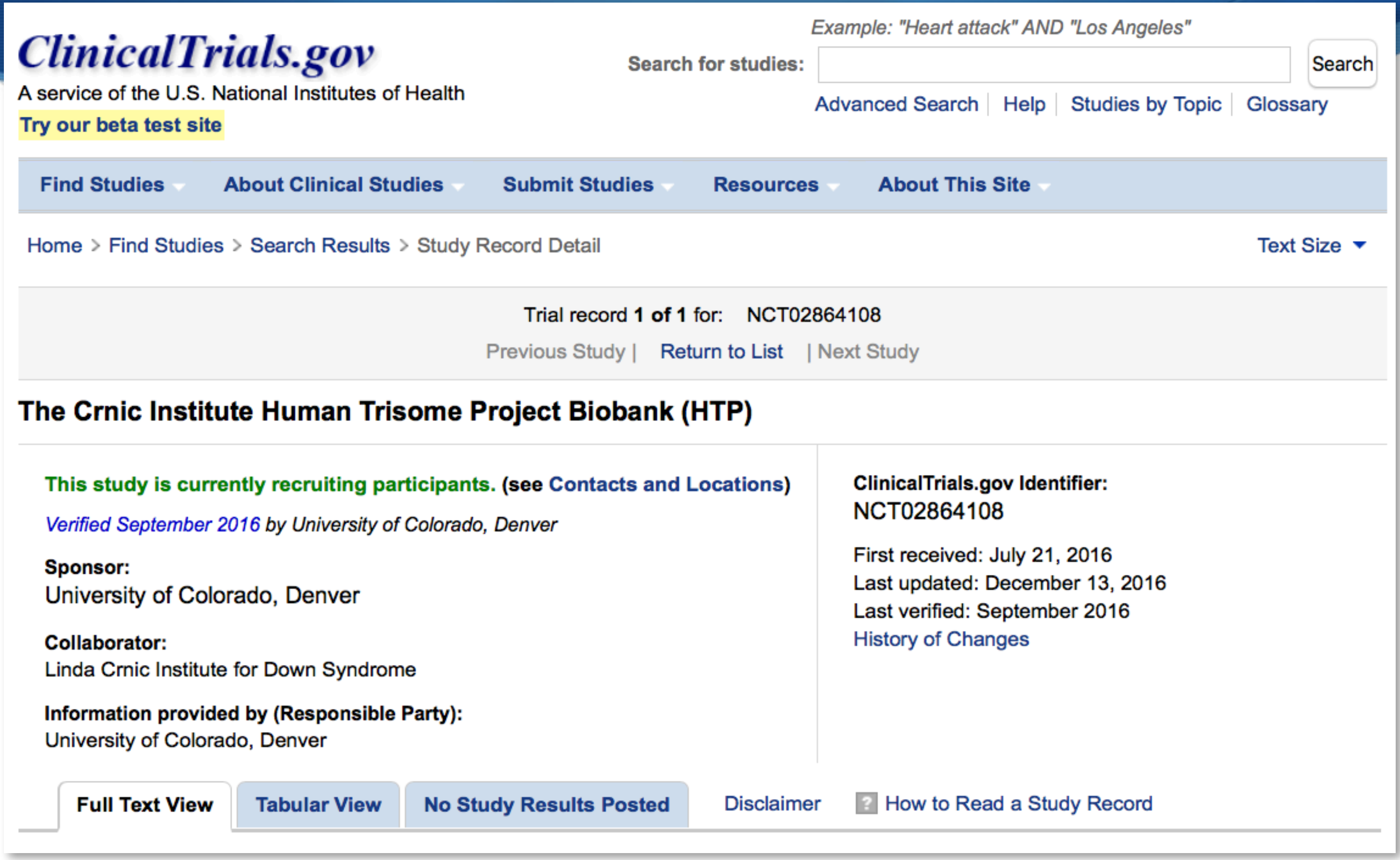
Contact Angela Rachubinski at 303-724-7366
or htp@ucdenver.edu

Compensation will be provided.

COMIRB#: 15-2170 **PI:** Joaquin Espinosa

Active protocol in clinicaltrials.gov

NCT02864108



Trial record **1 of 1** for: NCT02864108

The Crnic Institute Human Trisome Project Biobank (HTP)

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2016 by University of Colorado, Denver

Sponsor:
University of Colorado, Denver

Collaborator:
Linda Crnic Institute for Down Syndrome

Information provided by (Responsible Party):
University of Colorado, Denver

ClinicalTrials.gov Identifier:
NCT02864108

First received: July 21, 2016
Last updated: December 13, 2016
Last verified: September 2016
History of Changes

Frequently Asked Questions

Who can participate?

- Anyone ages 6 months – 89 years
  - Individuals with DS (if over 18 an LAR or equivalent must be provided), their parents and siblings
  - Individuals without DS

What happens when I join?

- Mouth swab
- Blood draw
- Participant survey
- Medical release for access to outside records
- Compensation is provided

Frequently Asked Questions

Other optional procedures

- Urine sample
- Stool sample
- Additional blood sample
- Return of research results
- Longitudinal data collection
- Information about additional studies

Frequently Asked Questions

What happens to my information?

- Your information is stored in HIPAA-compliant databases
- Only ‘de-identified’ information will be provided to researchers

What happens to Data, Tissue, Blood and Specimens that are collected?

- Both the investigators and sponsors of this research may study your data and samples
- Use of identified samples must have additional approval
- Any product or idea created by the researchers working on this study will not belong to you
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea

Frequently Asked Questions

What are the possible discomforts or risks?

- Typical risks associated with blood draw
- Potential loss of privacy

Is there a benefit for participants?

- Although there are no direct benefits to you, it may help future generations understand the unique issues associated with Down syndrome.

Can I change my mind?

Yes, absolutely. Your participation is voluntary at all times, You can withdraw at any time by contacting the study staff.

Thank You!

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