Collaborate to Accelerate Discoveries in Pediatric Research

Fall Webinar
September 29, 2022
3-5 pm ET

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What I Learned About the Kids First Program

Program Manager
Marcia Fournier, PhD

Gabriella Miller Kids First Pediatric Research Program
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Marcia Fournier @MarciaFournier2
Kids First Building a Resource to Bring Together Multiple Data Types Across Pediatric Conditions

- KF Data Resource Center allows for **multiple data types** and cross disease associations
  - Multiple data types allow a better view of the condition’s underlying biology
- Knowledge of **common biology across pediatric conditions** can speed up the development of diagnostics, treatments, and prevention tools.
- Kids First commitment to **sharing genomic data associated with clinical data** allows genetic variant search
  - within a single disease area or dataset
  - across diagnoses and cohorts
  - allow users to explore similar underlying causes of cancers, structural birth defects, and other rare disorders.
Kids First Started with Gabriella Miller Pediatric Cancer Advocacy Empowering Research Across Pediatric Conditions

Oct 2013
Gabriella Miller childhood cancer advocate died at 10 with Brain cancer

April 2014
Bipartisan bill Gabriella Miller Kids First Research Act signed by congress authorizes $12.6 million per year for ten years to NIH support pediatric research

Sept 2015
NIH Kids First Program first annual appropriation. The program is funded through 2024

NEW July 28, 2022
Gabriella Miller Kids First Research Act 2.0 passed House.
The Intersection of Human Development and Childhood Cancer as a Scientific Hypothesis

Shared mutation: BRAF, MAPK, ALK
The Kids First Working Group comes together across NIH to **build a cloud-based genomic data resource** to accelerate **collaborative research** leading to better prevention, diagnosis, and treatments for patients and families with pediatric cancer and structural birth defects.

**Kids First Working Group Members**

- National Institutes of Health (NIH)
- NIDCR
- NIAAA
- NINDS
- NIDDK
- NIEHS
- NEI
- NIAMS
- NIAID
- NCATS
- ORIP
- CDC
Kids First Empowered by X01 Mechanism, Genome Sequencing Centers, and Data Resource Center. All Starts with Patients Cohorts and Your Proposals

Submit Your Proposals to NIH X01 Mechanism

Release data to public after 6-month embargo

Selected X01 investigators receive access to generate genomic data at KF Sequencing Centers

Deliver data back to X01 investigators

KF Data Resource Center Performs Clinical Data Review and QC to compile genomes with phenotypes and clinical data

KF Sequencing Centers provide service to generate genomic data from DNA/RNA samples

Kids First Empowered by X01 Mechanism, Genome Sequencing Centers, and Data Resource Center. All Starts with Patients Cohorts and Your Proposals
The Kids First DRC performs **Clinical Data Reviews** to pair genomic and clinical datasets, producing a high-quality data resource for X01 investigators and secondary researchers.

**Kids First Data Delivery Status**

As of September 27, 2022 – KF DRC Data tracker

**X01 Projects - Clinical Data Review Status**

- FY15
- FY16
- FY17
- FY18
- FY19
- FY20
- FY21

- Approved
- In Review
- Not Started

As of September 27, 2022 – KF DRC Data tracker
How to Access the Kids First Data Today

Get Started at https://portal.kidsfirstdrc.org
Kids First’s Cloud-Based Platforms

**Kids First Data Resource Portal**  - [portal.kidsfirstdrc.org](http://portal.kidsfirstdrc.org)

- **EXPLORE** datasets and build cohorts of participants
- **DISCOVER** harmonized genomic data files for further research
- **CONNECT** data from multiple Kids First studies

**CAVATICA**  - [cavatica.sbgenomics.com](http://cavatica.sbgenomics.com)

- **COMPUTE** large scale workflows on genomic data files
- **ANALYZE** data in the cloud via R Studio and Python Notebooks
- **SHARE** tasks and findings with collaborators around the world
New Public Data Releases – Structural Birth Defects

- September 7, 2022, **Kids First Cornelia de Lange Syndrome (CdLS)**
  - CdLS is characterized by development delays, cognitive impairment, short stature, hearing loss, specific facial features, and structural birth defects such as differences of the limbs, heart, kidneys, and GI tract.
  - This work will lead to identify genetic causes and candidate genes for isolated birth defects seen in constellation in similar diagnoses.
  - Related Genes
    - SMC1A
    - NIPBL
    - HDAC8

- August 25, 2022, **Kids First Bladder Exstrophy, Epispadias, Complex (BEEC)**
  - BEEC describes a subset of anomalies with a spectrum of developmental defects.
  - Patients with BEEC suffer substantial morbidity and mortality due to impaired genito-urinary dysfunction.
  - Elucidating the underlying genetic component is critical to gaining a better understanding of the developmental signaling pathways and is likely the first step to developing targeted therapy.
  - Variants in genes identified in other urogenital anomalies appear to be responsible for some cases of BEEC including IS, WNT3, WNT9b, PLAG1 and p63.
  - Related genes
    - CELSR3
    - ISL1
    - OTX1
    - SLC20A1

PI: Ian Krantz, MD. Children’s Hospital of Philadelphia

PI: Angie Jelin, MD. Johns Hopkins University
New Public Data Releases – Childhood Cancers

- **September 26, 2022**, Gabriella Miller Kids First Pediatric Research Program in **Pediatric T-Cell Acute Lymphoblastic Leukemia**
- The outcome for patients with relapsed T-ALL is dismal with 3-year event free survival of <15%.
- The primary goal in the treatment of T-ALL is to prevent relapse, which requires accurate risk stratification. No genetic alterations have been identified to date that are reproducibly prognostic independent of minimal residual disease (MRD), making it difficult at diagnosis to identify which patients are more likely to relapse.
- Approximately 1350 cases of T-ALL from children and young adults treated on AALL0434 were selected for whole genome sequencing, whole exome sequencing, and transcriptome profiling (RNA-Seq) of tumor DNA/RNA and whole genome sequencing of germline DNA.
- Clinical Trials
  - [NCT00408005](#)

PI: David T. Teachey. Children's Hospital of Philadelphia
More Kids First Data Being Released Soon!

Structural Birth Defects
- Orthopaedic Disease (FY16, Rios) (N=300)
- Fetal alcohol spectrum disorder (FY18, Chambers) (N=236)
- Congenital heart disease (CHD) and acute leukemia in down syndrome (FY18, Lupo) (N=2816)
- Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) (FY19, Gharavi) (N=1530)
- Neural tube (FY19, Gleeson) (N=990)
- Orofacial clefts (FY19, Leslie) (N=560)
- Congenital heart defects (FY19, Martin) (N=545)
- Laterality defects (FY19, Ware) (N=760)

Cancer
- Chondrosarcoma malignant tumor from cartilaginous cells (FY17, Sobreira) (N=350)
- Pediatric germ cell tumors (FY18, Lau) (N=800)

>5000 Patient and Family Samples in Multiple Pediatric Conditions
Kids First Data Available Today

1. **56 sequencing projects**
2. **30 Publications**
3. **27 studies at dbGaP**
4. **515 data access requests approved to date**
Kids First is Part of a Larger Data Ecosystem

NIH Cloud-Based Platforms Interoperability (NCPI): Empower end-user analyses across platforms through federation & interoperability

Innovation across the Phenotypic Translational Divide Webinar Series
Focus for 2023

Add Data Types
- Genomics, Proteomics, Long Reads, Diversity in Cohorts

Enhance Data Sharing
- Discovery and Data Generation

Create More Collaborations
- Interoperability and Cross-Disease Focus
What is Important to Keep in Mind When Applying to X01

- Read and follow guidance from the program announcement!
  - Discovery of the Genetic Basis of Childhood Cancers and of Structural Birth Defects: Gabriella Miller Kids First Pediatric Research Program (X01 Clinical Trial Not Allowed)

- X01 gives access to generate genomic data
- Data have no use limitations or requirements
  - Data use does not require approval by an Institutional Review Board for secondary analyses
  - Data have no publication embargo
- The program prioritizes proposals for cohorts with rich phenotypic and clinical information
Small Research Grants for Analyses of Gabriella Miller Kids First Pediatric Research Data

- R03 small grant mechanism –PAR -19-375 (Due date for new submissions October 16, 2022)
  - Awards for up to 2 years
  - Budget expanded up to $100,000/year in direct costs
  - Preliminary data is not required

- Past opportunities: PAR-16-348, PAR-18-733, PAR-19-069
  - 97 applications received
  - 24 received funding

- Go shopping: https://grants.nih.gov/funding/searchguide/index.html#/
“Alleviate suffering from childhood cancer and structural birth defects by fostering collaborative research to uncover the etiology of these diseases and supporting data sharing within the pediatric research community”
How does your work relate to the webinar’s theme: “Growing Diversity of Data Types and Collaborative Research”
-“Work with multidimensional datasets and trans-disciplinary research teams to accelerate the pace of discoveries”
-“Through integrated analyses of the clinical profile, genome, transcriptome, proteome, metabolome, immune profile and microbiome of hundreds of individuals with Down syndrome compared to euploid controls, the HTP has enabled discoveries that have been translated into innovative clinical trials for Down syndrome in a very short amount of time”.

Joaquin Espinosa, PhD
Executive Director and Professor of Pharmacology

Linda Cnnic Institute for Down Syndrome
University of Colorado School of Medicine

The Power of Multidimensional Datasets and Collaborations to Accelerate Research
The power of multidimensional datasets and collaborations to accelerate research

The argument for developing interoperability mechanisms across NIH and beyond

Joaquín M. Espinosa, PhD
Linda Crnic Institute for Down Syndrome
INCLUDE Data Coordinating Center
Down syndrome: The ultimate challenge in precision personalized medicine

The chromosomal abnormality causing Down syndrome (i.e., trisomy 21) has been known since 1959.

Chromosome 21 was the first human chromosome to be sequenced, back in 2000, leading to the identification of ~225 genes.

No mutations, simply 1.5x gene dosage.

How have we used this information to improve the lives of people with Down syndrome?
People with Down syndrome have a differential ‘clinical risk profile’

Core phenotypes:
- Stunted growth
- Neurodevelopmental delays
- Dysmorphogenesis
- Atypical progeria

Somehow, an extra copy of chromosome 21 modulates the appearance and severity of major medical conditions:
- Cancer
- Atherosclerosis
- Hypertension
- Allergies
- Alzheimer’s
- Autoimmunity
- Leukemias
- COVID-19
- Congenital heart disease, autism, seizures disorders, and more…

The ~6 million human beings alive today with trisomy 21 may hold solutions to many major medical conditions.
Each one of them is dealing with trisomy 21 in their own unique, personal way

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

Our motto:

*Nothing in the study of Down syndrome makes sense except in the light of Personalized Medicine*
What drives this remarkable phenotypic variation?

Is it driven by genetic variants?

Is it driven by epigenetic mechanisms?

Are these different ‘phenotypes’ driven by different ‘endotypes’ manifested in the transcriptome, proteome, metabolome, microbiome, or immune profiles?

What are the roles for the environment, lifestyle, socio-economic status, and cultural factors?

Clearly, we need an orchestrated effort that would enable the testing of myriad alternative hypotheses quickly and efficiently…
The NIH INCLUDE Project

INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome

- Trans-NIH research initiative established in 2018 focused on critical health and quality-of-life needs for individuals with Down syndrome
- Quadrupled new funding for Down syndrome research since 2018
- Three areas of focus:
  1. High-risk high-reward basic science
  2. Assembly of a large cohort study across the lifespan
  3. Inclusion of individuals with Down syndrome in clinical trials
The Crnic Institute Human Trisome Project (HTP)

A pan-omics natural history study of Down syndrome with a multidimensional biobank, and a public researcher portal

www.trisome.org

Thousands of datasets generated

- 900+ Clinical histories
- 400+ Genomes
- 500+ Transcriptomes
- 500+ Metabolomes
- 400+ Immune maps
- 500+ Microbiomes

TrisomExplorer

The TrisomExplorer enables easy access to all data generated by the Human Trisome Project through this user-friendly portal, amenable to both scientists and the general public.

More than 900 participants recruited since 2016!

30+ Projects supported
20+ Papers published / under review
The importance of multidimensional biobanking

All these samples are obtained from a single interaction with the research subject.
What are the impacts of trisomy 21 on?:

- The transcriptome
- The proteome
- The metabolome
- The immune cell repertoire
- The microbiome
- The global autoantibody profile
- The epigenome
- The functional genome
- And more…

Multidimensional biobanks lead to multidimensional datasets for collaborative discoveries of multidimensional impact
Everywhere we looked, it was clear that trisomy 21 causes increased interferon signaling

- Cell Lines
- Primary Samples

- Transcriptome
- Proteome
- shRNA Screens
What is interferon signaling?

- Interferon signaling is an important part of the immune system involved in the anti-viral defense.
- Interferon signaling activates many different types of immune cells.
- Interferon hyperactivity is a known risk factor for autoimmunity.
There are three major types of IFN signaling, involving different ligands and receptors.

Interferons require the JAK1 enzyme to function.

Interferon signaling mounts the antiviral response.

ISG: Interferon-Stimulated Gene
The largest transcriptome analysis of people with Down syndrome to date

400 ‘whole blood’ (PAXgene RNA) transcriptomes, 304 with trisomy 21

The blood of people with Down syndrome looks like is fighting a viral infection...

Galbraith et al, under review
The blood of people with Down syndrome looks like it is fighting a viral infection 24/7.

IFN scores are commonly used to monitor the degree of IFN activity.

A gene expression score composed of 18 ISGs, comparing samples with trisomy 21 versus COVID-19.

Galbraith et al, under review
What drives interferon hyperactivity in Down syndrome? 4 of the 6 interferon receptors are encoded on chr21!!!
4 of the 6 IFN receptors are encoded on chr21!!

Whole blood RNAseq, 400 samples, 304 with trisomy 21

Galbraith et al, under review
4 of the 6 IFN receptors are encoded on chr21!!

Whole blood RNAseq, 400 samples, 304 with trisomy 21

Individuals with trisomy 21 over-express interferon-stimulated genes (ISGs)

Galbraith et al, under review
What is the impact of trisomy 21 on the circulating proteome?

Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation

Kelly D. Sullivan1,2, Donald Evans1, Ahwan Pandey1,2, Thomas H. Hraha3, Keith P. Smith1, Neil Markham1, Angela L. Rachubinski4, Kristine Wolter-Warmerdam5, Francis Hickey6, Joaquin M. Espinosa1,2,6 & Thomas Blumenthal1,6,7

2017

SOMAscan® proteomics
The plasma of people with Down syndrome looks like that of someone affected by an autoinflammatory condition

Plasma proteomics analysis of 419 research participants (316 with trisomy 21) in the Human Trisome Project

GSEA: proteome changes in trisomy 21 versus euploid controls

TFF1: a protein encoded on chromosome 21
SAA1: an inflammatory marker
People with Down syndrome show much elevated levels of IFN-inducible (and many other) cytokines

Cytokine analysis of 468 research participants (337 with trisomy 21) in the Human Trisome Project

Mixed linear model adjusting for age, sex and sample source

Galbraith et al, under review
What is the impact of trisomy 21 on the immune cell repertoire?

High resolution mapping of the immune system in Down syndrome
Employing CyTOF technology to map the immune system of people with Down syndrome

Mass Cytometry Reveals Global Immune Remodeling with Multi-lineage Hypersensitivity to Type I Interferon in Down Syndrome

Mass cytometry reveals global immune dysregulation among individuals with trisomy 21

Kernal Density Estimate (KDE) of viSNE plots to quantitatively compare densities:

Waugh et al, Cell Reports 2019
Key findings:

- Increased in Down syndrome

- Decreased in Down syndrome

- Immune homeostasis

- IFNR expression
  - IFN signaling
  - Fibrocytes
  - Inflammatory monocytes
  - Activated NK cells
  - Activated cytotoxic T cells
  - Plasmablasts

HSPCs
- Classical Monocytes
- Naive cytotoxic T cells
- Immature B Cells
- IgM Memory B cells

Waugh et al, Cell Reports 2019
Widespread overexpression of IFNRs across the immune system of people with Down syndrome

IFNAR1 surface protein expression (CyTOF)

IFNAR2, IFNGR2 and IL10RB are also overexpressed in cells with trisomy 21

Waugh et al, Cell Reports 2019
People with Down syndrome are hypersensitive to interferon stimulation

*Ex vivo* IFN$\alpha$ stimulation of fresh blood samples
STAT phosphorylation measured by CyTOF

Immune cells with trisomy 21 are ‘super-responders’ to interferon

Waugh et al, Cell Reports 2019

D21: euploid controls
Trisomy 21 cells are hypersensitive to interferons

• Dose-response experiment \textit{in vitro}

• Skin fibroblasts with and without trisomy 21

• MX1 and ISG15 are canonical ISGs

• Cells with trisomy 21 show both, higher \textit{basal} expression and higher \textit{induced} expression of ISGs

• Not just immune cells, IFN signaling works throughout the body!
What are the impacts of trisomy 21 on the metabolome?

Employing mass-spectrometry approaches to map the metabolic impacts of trisomy 21

Trisomy 21 activates the kynurenine pathway via increased dosage of interferon receptors

Rani K. Powers1,2,3, Rachel Culp-Hill4, Michael P. Ludwig1,3, Keith P. Smith1, Katherine A. Waugh1, Ross Minter1, Kathryn D. Tuttle1, Hannah C. Lewis1, Angela L. Rachubinski1,5, Ross E. Granrath6, Maria Carmona-Iragui6,7, Rebecca B. Wilkerson6, Darcy E. Kahn1, Molishree Joshi1, Alberto Lleo6, Rafael Blesa6, Juan Fortea6,7, Angelo D•Alessandro1,4, James C. Costello2,3, Kelly D. Sullivan1,3,8,9 & Joaquin M. Espinosa1,3,8,9.
People with Down syndrome display activation of the kynurenine pathway

Plasma metabolomics measuring 91 metabolites
120 participants, 72 with trisomy 21

Powers et al, Nature Comms 2019
Quinolinic acid, the inescapable neurotoxin

• Quinolinic acid (QA) is super-agonist of NMDA receptors
• QA induces excitatory toxicity
• Memantine (an NMDR antagonist) protects from QA-mediated neurotoxicity in mice
• Circulating levels of QA were associated with lower cognition in older adults with AD in the typical population
• QA is a potent convulsant involved in the etiology of epilepsy and seizures, which are more common in Down syndrome
People with Down syndrome overexpress IDO1, the rate-limiting enzyme in the kynurenine pathway. Kynurenine dysregulation correlates positively with levels of IFN-inducible cytokines such as IP-10.
Conclusion:

Down syndrome could be understood, in good measure, as an Interferonopathy.

What is an Interferonopathy?
Interferonopathies are a group of genetic disorders characterized by upregulation of the interferon response:

Aicardi-Goutieres Syndrome, SAVI, CANDLE, Singleton–Merten syndrome, spondyloenchondrodysplasia, dyschromatosis symmetrica hereditaria, familial chilblain lupus, Nakajo-Nishimura syndrome, spondylochondromatosis, etc.

Many features shared with Down syndrome:

- Severe neurological dysfunction
- Severe developmental delay
- Less white matter in the brain
- Seizures
- Cerebellar atrophy
- Spastic diplegia, a form of cerebral palsy (CP), a chronic neuromuscular condition of hypertonia and spasticity
- Dystonic posturing
- Hyper- or hypotonia
- Profound psychomotor difficulties
- Thrombocytopenia (deficiency of platelets)
- CSF lymphocytosis (too many white blood cells in the spinal fluid)
- Systemic immune abnormalities, strong predisposition to autoimmunity
- Hypocomplementia
- Common skin lesions (e.g., acrosy anosis)
Would drugs that inhibit interferon signaling improve health outcomes in Down syndrome?
FDA-approved therapies that decrease the interferon response: JAK inhibitors

<table>
<thead>
<tr>
<th>Company</th>
<th>Marketed Name</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lilly</td>
<td>Olumiant® (baricitinib) tablets</td>
<td>JAK1&amp;2</td>
<td>Rheumatoid arthritis (2018), COVID-19 (2022), alopecia areata (2022)</td>
</tr>
<tr>
<td>Abbvie</td>
<td>RINVOQ® (upadacitinib tablets)</td>
<td>JAK1</td>
<td>Rheumatoid arthritis (2019)</td>
</tr>
</tbody>
</table>

Could JAK inhibitors ‘normalize’ the immune system in Down syndrome? If so, what could be the potential benefits?
Clinical trial for JAK inhibition in Down syndrome

Targeting five autoimmune skin conditions in one trial

All five conditions are more prevalent in Down syndrome

~25% of adults with Down syndrome have been affected at some point by one of these conditions

4-9 months of treatment with an FDA-approved JAK inhibitor: Tofacitinib (Xeljanz)
Study Objectives and Design

- Individuals with Down syndrome ages 12 - 50
- Phase II, single arm, open label
- 16-week treatment with Tofacitinib
  - Optional 24-week Extension Arm
- Moderate-to-severe autoimmune skin condition:
  - Psoriasis
  - Hidradenitis suppurativa
  - Vitiligo
  - Atopic dermatitis
  - Alopecia areata (affecting at least 25% of scalp)

**Aim 1:** Define the safety profile in Down syndrome.

**Aim 2:** Determine the impact on immune dysregulation.

**Aim 3:** Define the impact on immune skin conditions.

**Aim 4:** Characterize impact on cognition and quality of life.
Top level results

Analysis of first 10 participants

- **Zero** serious adverse events
- 6/6 participants with alopecia areata experienced hair regrowth, to varying degrees
- 2/2 participants with atopic dermatitis saw complete remission
- 1/1 participant with psoriasis saw complete remission
- 2/5 participants showed improvements in hidradenitis suppurativa
Top level results

Benefits going well beyond skin deep!

- All participants showed decreased inflammatory markers

- 7/7 participants with clinically significant anti-thyroid autoimmunity displayed decreased levels of autoantibodies

- Improvements in one measure of spatial memory, one measure of visuomotor function, and anxiety/depression scores…
Male, 17 years old, alopecia areata

When a picture is worth a thousand words

Baseline
SALT = 86

Participant known to the research team as 'Ed Sheeran'
Male, 40 years old – Psoriatic arthritis

When a picture is worth a thousand words

Baseline

Post-treatment

Participant monitored outside of the trial at the University of Vermont Medical Center
**Significant decrease in the autoimmune attack to the thyroid gland**

Autoimmune thyroid disease is the most common autoimmune condition in Down syndrome.

All 7 participants with ‘clinically significant’ anti-TPO antibodies displayed decreases in autoantibody levels.

Values above 60U/mL are ‘clinically significant’.

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**Graph:**
- **X-axis:** Baseline, Week 2, Week 8, Week 16, Post Rx
- **Y-axis (anti-TPO):** Logarithmic scale
  - Baseline: Red dots
  - 16 week: Teal dots
  - Upper normal limit (NCS): Dashed line
  - NCS: <60 U/mL
- **Statistical Information:**
  - \( n = 7 ; \ p = 0.00118 \)
Female, 28 years old
Down Syndrome Regression Disorder

Clear improvement in visuomotor function as measured by the NEPSY II test
Down syndrome Regression Disorder (DSRD)

- A rare but devastating condition characterized by sub-acute onset of catatonia, mutism, depersonalization, loss of ability to perform activities of daily living, hallucinations, delusions, and aggression.

- A subset of DSRD cases are associated with neurodiagnostic abnormalities indicative of immune dysregulation affecting the central nervous system (CNS), often associated with preceding immune trigger events.

- Is DSRD an autoimmune condition, akin to autoimmune encephalitis?
Clinical trial for mechanistic investigation of therapies for Down syndrome Regression Disorder

Goal: To compare the safety and efficacy of two ‘immune therapies’ (one of them a JAK inhibitor) versus a psychiatric medicine (a benzodiazepine).

Multi-site collaboration between the Crnic Institute, Children's Hospital Colorado, and Children’s Hospital Los Angeles.

Santoro
Neuroimmunology

Sannar
Psychiatry

Patel
Psychology

Kammeyer
Neuroimmunology

Sanders
Neurology

Rachubinski
Crnic

Espinosa
Crnic (contact PI)

NIH

THE INCLUDE PROJECT

NIH

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Coming in 2023…
Tofacitinib normalizes interferon signaling without overt immune suppression

Comparison of the clinical trial participants to those in the Human Trisome Project:
1. The clinical trial cohort shows ‘average’ IFN scores for people with Down syndrome at baseline
2. Tofacitinib treatment brings IFN scores down to the range observed in typical people
3. Indicates therapeutic benefit without overt immune suppression
Research Participant ‘X’

Female, 22-24 years old at time of blood draws, complete trisomy 21, taking Tofacitinib ‘on and off’ since 2016 for alopecia areata

Schedule of research blood draws:

- 2017:
  - 4 weeks 10 mg
  - 4 weeks 5 mg
  - 6 weeks Off
  - 6 weeks 10 mg
  - 4 weeks Off

- 2018:
  - 5 weeks Off
  - 8 weeks Off
  - 4 weeks 10 mg
  - 32 weeks 5 mg

- 2019:
  - Ongoing 10 mg

Participant X provided 10 research blood draws while being on and off Xelajnz.
Tofacitinib reduces IFN scores down to the ‘typical range’

The medicine ‘normalizes’ IFN scores, bringing them down to the range observed in the general population, thus preserving immune activity.
Multidimensional datasets shrink the translational timeline!

Idea
- Identify Target

Basic Research
- Identify Target

Pre-Clinical Research
- Validate Target
- Develop Therapeutic

Clinical Trials
- Test Safety
- Test Efficacy

Regulatory Approval & Medical Care

2016 → 2020

Trisomy 21 consistently activates the interferon response

Kelly D Sullivan¹,²,³,⁴, Hannah C Lewis¹,², Amanda A Hill¹,², Ahwan Pandey¹,²,³,⁴, Leisa P Jackson¹,³,⁴, Joseph M Cabral¹,³,⁴, Keith P Smith¹, L Alexander Liggett¹,⁵, Eliana B Gomez¹,³,⁴, Matthew D Galbraith¹,²,³,⁴, James DeGregori¹,⁵,⁶,⁷,⁸,⁹, Joaquin M Espinosa¹,²,³,⁴,⁵

Tofacitinib for Immune Skin Conditions in Down Syndrome
ClinicalTrials.gov Identifier: NCT04246372

Recruitment Status: Recruiting
First Posted: January 29, 2020
Last Update Posted: February 16, 2021
See Contacts and Locations
What are all the potential benefits of treating the interferonopathy of Down syndrome?

Normalization of IFNR copy number in mice attenuates:
- Immune hypersensitivity
- Congenital heart disease
- Craniofacial abnormalities
- Cognitive impairments


doi: https://doi.org/10.1101/2022.02.03.478982
Conclusions

• Interferon hyperactivity can cause many health issues in individuals with Down syndrome, such as autoimmune disorders and severe complications from lung viral infections (e.g., COVID19).

• Research into immune system dysregulation in Down syndrome has illuminated therapeutic strategies being tested in first-in-kind clinical trials (e.g., JAK inhibition)

• Restoring immune balance could have multidimensional benefits in Down syndrome.
Back to multidimensionality and interoperability: Where is the data driving these discoveries?

Genome data:

Transcriptome data:

Proteome data:

Metabolome data:

Mass cytometry data:  

Clinical metadata:

Biospecimen data?

Animal model data?

Clinical trial data?

This is a nightmare, a very cumbersome and inefficient system
Empowering multidimensional research through the INCLUDE Data Hub

All HTP data in one place!
Empowering multidimensional research through the INCLUDE Data Hub

All HTP data in one place!
Empowering multidimensional research through the INCLUDE Data Hub

All HTP data in one place!
Empowering multidimensional research through INTEROPERABILITY!

How to enable seamless use of these multiple resources?
Credits

Crnic Institute team:
Kelly Sullivan
Matthew Galbraith
Angela Rachubinski
Katie Tuttle
Ross Minter
Kate Waugh
Paula Araya
Jessica Baxter
Kydal Schade
Michael Ludwig
Keith Smith
Amanda Hill
Belinda E. Estrada
Belinna Guerra
Pamela Navarrete
Ross Granrath
Kayleigh Worek
Jessica Shaw
Neetha Eduthan
Kohl Kinning
Monica Lintz
Lyndy Bush
Chelsea Donohue
Anne Fiala
Haley Sanders
Zdenek Andrysik
Eleanor Britton
Hannah Lyford
And so many more!

JAKi trial team:
David Norris
Cory Dunnick
Liz Wallace
Emily Gurnee
Debbie Fidler
Lina Patel

DSRD team:
Jon Santoro
Elise Sannar
Lina Patel
Jessie Sanders
Ryan Kammeyer

INCLUDE DCC team:
Brian O’Connor
Melissa Haendel
Robert Carroll
Vincent Ferretti
Adam Resnick
Jack DiGiovanna
Huiqing Li (NHLBI)
Charlene Schramm (NLHBI)
Gail Pearson (NHLBI)
Melissa Parisi (NICHD)
Sujata Bardhan (NICHD)
Valerie Cotton (NICHD)
Laurie Ryan (NIA)
Erika Tarver (NIA)
And so many more!

Many many collaborators at the University of Colorado

The amazing team at the Global Down Syndrome Foundation
How does your work relate to the webinar’s theme: “Growing Diversity of Data Types and Collaborative Research”
- “Project initiated many collaborations with researchers from different areas of expertise and of different backgrounds”
- “Project has enabled the training of many minority students including graduate students, postdocs and residents in the field of genomics”

How do you hope to impact the audience?
- “Understanding the importance of genomics in the field of rare disease and cancer and how these fields can help each other to find more effective pharmacological treatments for our patients”

Nara Sobreira, PhD
Assistant Professor of Genetic Medicine & Pediatrics
Johns Hopkins University School of Medicine

Cross Disease Analysis
Pediatric Cancer and Structural Birth Defects

Interoperability using CCDI and CBTN
Genome-wide Sequencing Analysis to Identify the Genes Responsible for Enchondromatosis and Related Malignant Tumors

Nara Sobreira, MD, PhD
Johns Hopkins University
McKusick-Nathans Department of Genetic Medicine
Enchondromatoses disorders

- Metaphyseal enchondromatosis with D-2-hydroxyglutaric aciduria (MEHGA) — enchondromas, elevated D-2HG, short bones, macrocephaly, developmental delay
- Genochondromatosis (AD)
- Dysspondyloenchondromatosis (AD - COL2A1)
- Spondyloenchondrodysplasia with immune dysregulation (AR - ACP5)
- Metachondromatosis (AD – PTPN11)
**Enchondromatosis disorders**

- Ollier disease (OMIM 166000) – multiple enchondromas
- Maffucci syndrome (OMIM 614569) – enchondromas and vascular anomalies
- In both disorders there is a ~30% risk of chondrosarcoma transformation

Jermann et al., 2001
Ollier disease (286 patients) Maffucci syndrome (235 patients)

- 77 (27%) chondrosarcoma
- 29 (10%) gliomas
- 13 (4.5%) gonadal malignancy
- 1 (0.34%) vascular malignancy

- 74 (31.5%) malignancy
- 9 (3.8%) malignancy
- 9 (3.8%) malignancy
- 17 (7.2%) malignancy

Percentage of patients with malignancies.
Molecular bases of Ollier disease and Maffucci syndrome

- OD and MS occur as isolated cases
- No familial cases have been reported to date, and no germline variants have been compressively investigated in these patients thus far
- Gain-of-function, somatic variants in IDH1 (p. Arg132His, p.Arg132Cis, and p.Arg132Ser) and IDH2 (p.Arg172Ser) have been identified in ~80% of the tumors (enchondromas, chondrosarcomas, and vascular anomalies) of individuals with OD and MS but not in blood or unaffected tissue
Molecular bases of Ollier disease and Maffucci syndrome

- OD and MS occur as isolated cases

Ollier disease and Maffucci syndrome are cancer predisposition syndromes caused by germline or early postzygotic variants and subsequent hits in the same or different genes lead to formation of enchondromas, vascular anomalies, and chondrosarcomas

with OD and MS but not in blood or unaffected tissue
Molecular bases of Ollier disease and Maffucci syndrome

- We analyzed germline WES and/or WGS on 94 patients, 71 with OD and 23 with MS (68 trios)

- Baylor-Hopkins Center for Mendelian Genomics and Gabriella Miller Kids First project

- We identified rare (minor allele frequency [MAF] <1%) candidate causative variants in 6 genes (HIF1A, VHL, IDH1, IDH2, KDM4C, and CDKN2A) related to the HIF-1 pathway in approximately 22% of the probands [21/94 total, 14/71 OD (~20%) and 7/23 MS (~30%)]

Molecular bases of Ollier disease and Maffucci syndrome

<table>
<thead>
<tr>
<th>Group</th>
<th>Proband samples</th>
<th>Control samples</th>
<th>p (FET)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With HIF1A variants</td>
<td>7</td>
<td>37</td>
<td>0.002</td>
<td>4.3 (1.9 to 10.1)</td>
</tr>
<tr>
<td>Without HIF1A variants</td>
<td>87</td>
<td>2017</td>
<td>0.002</td>
<td>4.3 (1.9 to 10.1)</td>
</tr>
<tr>
<td>With VHL variants</td>
<td>6</td>
<td>8</td>
<td>1.36e-05</td>
<td>17.4 (5.9 to 51.3)</td>
</tr>
<tr>
<td>Without VHL variants</td>
<td>88</td>
<td>2046</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With IDH1 variants</td>
<td>3</td>
<td>11</td>
<td>0.02</td>
<td>6.1 (1.6 to 22.3)</td>
</tr>
<tr>
<td>Without IDH1 variants</td>
<td>91</td>
<td>2043</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Six genes related to the HIF-1 pathway

**NORMOXIA**

- PHD2 (EGLN) → O$_2$-dependent proline hydroxylation → HIF-1α* → poly-ubiquination → proteasomal degradation

**HYPOXIA**

- HIF-1α* → HIF-1β → Transcript factor complex formation → HRE → Transcription of genes:
  - Angiogenesis
  - Erythropoiesis
  - Metabolism
  - Cell survival

Regulation of HIF-1α degradation at normoxia and hypoxia. * Genes found mutated in patients with OD or MS.
IDH1, IDH2 and HIF-1 pathway

Effect of GoF IDH1 and IDH2 variants in KDM4C and HIF-1α.

* Genes found mutated in patients with OD or MS.
Are genes in the HIF-1 pathway mutated in patients with isolated gliomas and chondrosarcomas?

- Access WGS data from 816 patients from the Pediatric Brain Tumor Atlas (CBTN and PNOC)
  - Data will be accessed through the Kids First Program Data Resource Center and CAVATICA
- Access WGS data from 383 patients with Osseous and Chondromatous Neoplasms from TARGET-OS project
  - Data will be accessed through the National Cancer Institute GDC Data Portal
- Access WGS data from patients with osteosarcoma and Ewing Sarcoma
  - dbGAP access to WGS from 13 patients from the Osteosarcoma Genomics project
  - WGS from Kids First Osteosarcoma project
  - WGS from Kids First: Ewing Sarcoma - Genetic Risk project
# Pediatric Brain Tumor Atlas Datasets

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Description</th>
<th>Probands</th>
<th>VCF Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBTN</td>
<td>CRDC dataset (within CCDI)</td>
<td>998</td>
<td>783 (harmonized pipeline)</td>
</tr>
<tr>
<td>PNOC</td>
<td>Kids First Collaborator dataset</td>
<td>79</td>
<td>33 (harmonized pipeline)</td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td>Already accessible through CAVATICA</td>
</tr>
</tbody>
</table>
Acknowledgments

- Nara Sobreira’s lab
  - Renan Martin
  - Elizabeth Wohler
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  - Carolina Montano
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  - Erika Kim
- NIH – NCI
- Patients and Families

Baylor-Hopkins Center for Mendelian Genomics

Kids First

National Human Genome Research Institute

National Cancer Institute
Hakon Hakonarson, MD, PhD
Director of the Center for Applied Genomics
University of Pennsylvania Perelman School of Medicine

Resolution of Disease Phenotype-Genotype Correlations in a Pediatric Cohort with Congenital Anomalies and Cancer
RESOLUTION OF DISEASE PHENOTYPE-GENOTYPE CORRELATIONS IN A PEDIATRIC COHORT WITH CONGENITAL ANOMALIES AND CANCER

HAKON HAKONARSON, MD PHD

PHILADELPHIA, 29 SEPTEMBER, 2022
• NIH funded X01 provides WGS for pediatric cohorts with birth defects (BD) or pediatric-onset cancer

• **Childhood cancers** and **structural birth defects** have profound, lifelong effects on patients.

• A risk factor for childhood cancer is being born with a birth defect (suggesting shared genetic pathways)

• The Kids First Data Resource allows scientists to identify genetic pathways underlying these conditions and to explore some of these pathways that are shared between them.

• These findings have the potential to improve prognostics and treatment decisions for childhood cancers
Cohort Selection from CAG Biorepository

• Selected all patients from the CAG biobank for co-occurrence of pediatric onset cancer and a birth defect based on ICD9 codes from CHOP EMR

• CHOP EMR for co-occurrence of ICD9 codes
  • Cancer: 230 ≤ ICD9 < 240 or 140 ≤ ICD9 < 211
  • Birth Defects: 740 ≤ ICD9 < 758

• 1464 probands (141 trios) with a wide range of phenotypes across both BD and cancer

CAG: Center for Applied Genomics @CHOP
Cohort Demographics

- **Age distribution**
  - Female: 513
  - Male: 757

- **Race**
  - White: 706
  - Male: 757
  - Female: 517
  - Asian: 12
  - Other: 61
  - Black/AA: 123

- **Family structure**
  - Female: 706
  - Male: 757
  - Trio: 18
  - Other: 70
  - Single: 669
Data Modalities

- 30x Whole Genome Sequence data (Broad)
  - Annotated using Cyclo/KnowVar (developed at CAG)
- Phenotypes:
  - Automated HPO conversion and scoring using SORTA / AWS Comprehend Medical
- Copy number Variants
  - Sequence-based calls using consensus from multiple callers
  - Array-based calls using parseCNV-clinical (developed at CAG)
- GD-Cross used to rank variants by pathogenicity and patient phenotype
  - In house variant prioritization tool (developed at CAG)
- Visualize large structural rearrangements and detect mosaics using custom B-allele frequency plots
- Mitochondrial sequence analysis
- Expansion repeat detection (bioinformatic)
Analytical Pipeline for Individual Cases

Step 1: Data Curation, Tool Development and Benchmarking

- VCF
- HPOs
- Multi CNV Caller

GDCross → Ranked list of SNVs and Consensus CNVs

WGS → 1,806 Samples

Clinical laboratory results → Clinical molecular diagnosis

Step 2: Downstream Analysis, Functional Validation and Discovery
Discovery pipeline

Noncoding regions
Burden analysis
HPO clustering
Pathway analysis
Phenotype Risk Score

Novel candidates

GeneMatcher
CHOP Zebrafish Core
iPS cells
Mouse Models
Target Analysis
Wide variety of cancer types. Major categories: nervous system cancers, neurofibromas, leukemias.

NV, nervous system
CDV, cardiovascular
MSK, musculoskeletal
DIG, digestive system
GNU, genitourinary
RES, respiratory
Summary of Molecular Diagnoses

Aneuploidy
- Female: 18
- Male: 12
- Trisomy 21: 13
- Trisomy 18: 1
- Trisomy 18 (mosaic): 1
- Trisomy 9 (mosaic): 1
- Turner syndrome (mosaic): 2
- Turner syndrome (mosaic)/monosomy Xp: 1
- Klinefelter syndrome: 1
- Ellis-van Creveld syndrome (UPD4): 1

Homozygous Hemizygous: 17%
- Missense: 184
- Nonsense: 83
- Frameshift: 40
- Large genomic alterations: 76
- In-frame deletion: 5
- Splice Site: 17
- Other: 14
- >30 M: 1

Heterozygous: 83%
- Missense: 184
- Nonsense: 83
- Frameshift: 40
- Large genomic alterations: 76
- In-frame deletion: 5
- Splice Site: 17
- Other: 14
- 20-100 KB: 3
- 1-5 KB: 4
- 10-20 M: 7
- 1-10 M: 13
- 100 KB-1 M: 8
- 1-10 M: 13
Pathway Analysis

Birth Defect

WikiPathway ID

KEGG ID

GO ID

Birth Defect and Cancer

WikiPathway ID

KEGG ID

GO ID
Single Molecular Diagnosis for Both Congenital Anomaly and Cancer

<table>
<thead>
<tr>
<th>Patient</th>
<th>Genes</th>
<th>Syndrome</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>KF5514560116</td>
<td>MNX1</td>
<td>Currario Syndrome</td>
<td>Sacrococcygeal teratoma, Anorectal malformation, neuroenteric cyst, tethered cord</td>
</tr>
<tr>
<td>KF6924243010</td>
<td>WT1</td>
<td>Denys-Drash Syndrome</td>
<td>Nephroblastoma, Indeterminate sex</td>
</tr>
<tr>
<td>KF6015867582</td>
<td>PORCN</td>
<td>Focal dermal hypoplasia</td>
<td>Laryngeal papilloma, Micro/anophthalmos, congenital heart defect, microcephaly</td>
</tr>
</tbody>
</table>
Dual Molecular Diagnoses

- Neoplasm of the lung
- Pleuropulmonary blastoma
- Multiple pulmonary cysts
- Abnormal lung morphology
- Global developmental delay
- Mitral regurgitation
- Mitral valve prolapse

**DICER1**
c.2040+1G>C
Pleuropulmonary blastoma

**TGFB2**
p.R299W
Loeys-Dietz syndrome 4
Dual Molecular Diagnoses
Copy-number and structural variations in WGS data

12.8 Mb
Multi-gene deletion

10.0 kb
Multi-exon deletion

3.1 kb
Single-exon deletion
Machine Learning Approaches to Finding CNV/SV

Signature patterns can be used to train machine-learning algorithms to highlight events that are difficult to detect by other means.
Conclusions

• Unique dataset in its phenotypic diversity
• HPO based phenotyping in a diverse set allows for alternate view to highly focused diagnosis-specific cohorts
• Complexity of the dataset has required development of infrastructure to support the analysis
• EMR-based phenotyping methods in rare disease cases and clustering for burden analyses
• Methods to visualize large SVs and extension of those methods to high-throughput AI-based approaches
• Development of our variant prioritization program, GDcross, to deal with cases of second hits, incorporate CNV calls into the prioritization and extend the scoring to non-coding regions

• Combined, the data and infrastructure we’ve built will lead to the identification of novel developmental / neoplastic pathways
Acknowledgement

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Haijun Qiu, PhD
Edward Liu, PhD
Xiao, Chang, PhD
John Connolly, PhD
Huiqi Qu, MD, PhD
Kids First Data Resource Center Cross Disease Availability, Accessibility and Secondary Use

David Higgins, PhD
Informatics Program Manager
Center for Data Driven Discovery in Biomedicine
Children’s Hospital of Philadelphia
Kids First Data Resource Center: Cross-Disease Availability, Accessibility, and Secondary Use

Kids First Fall Public Webinar
September 29th, 2022

Follow @kidsfirstdrc
Visit kidsfirstdrc.org
Data Resources - Released Datasets

Structural Birth Defects Studies (9,701)
  Congenital Diaphragmatic Hernia (2242)
  Congenital Heart Defects (2133)
  Kidney and Urinary Tract Defects (132)
  Orofacial Cleft - European Ancestry (1414)
  Orofacial Cleft - Latin American Ancestry (804)
  Syndromic Cranial Dysinnervation (801)
  Orofacial Cleft - African & Asian Ancestry (759)
  Cornelia de Lange Syndrome (373)
  Adolescent Idiopathic Scoliosis (314)
  Disorders of Sex Development (300)
  Craniofacial Microsomia (245)
  Microtia in Hispanic Populations (184)

Pediatric Cancer Studies (5,768)
  Neuroblastoma (1681)
  T-Cell Acute Lymphoblastic Leukemia (1358)
  Ewing Sarcoma (1168)
  Novel Cancer Susceptibility from BASIC3 (733)
  Familia Leukemia (620)
  Osteosarcoma (129)
  Enchondromatoses (79)

Released on the Kids First Portal

56,212 files
13,738 participants
>1.5 PB of data

With harmonized clinical diagnoses, phenotypes, and demographics
Data Resources - Funded Datasets

**Structural Birth Defects Studies (13,110)**
- Bladder Exstrophy, Epispadias, Complex (425)
- CHARGE Syndrome (545)
- Kidney and Urinary Tract Defects (1530)
- Congenital Diaphragmatic Hernia (1804)
- Congenital Heart Defects and Down Syndrome (1408)
- Esophageal Atresia (950)
- Genetics of Fetal Alcohol Spectrum Disorders (236)
- Hear-N-Seq - Hearing Loss (437)
- Laterality Birth Defects (760)
- Neural Tube Defects (960)
- Nonsyndromic Craniosynostosis (1140)
- Orofacial Cleft - Philippines (560)
- Orofacial Cleft - Puerto Rico, Cen. & S. America (214)
- Structural Brain Defects (1150)
- Valvar Pulmonary Stenosis (891)
- Vascular Anomalies (300)

**Pediatric Cancer Studies (6,789)**
- ALL and Down Syndrome (1408)
- Extracranial Germ Cell Tumors (120)
- Ewing Sarcoma (785)
- Infantile Hemangioma (300)
- Intracranial Germ Cell Tumors (800)

Funded for **21,761 additional samples** to be released in the future.
Apply for Access on dbGaP

Gabriella Miller Kids First Pediatric Research Project in Microtia in Hispanic Populations

dbGaP Study Accession: phs502172.v1.p1

Study Description

The Gabriella Miller Kids First Pediatric Research Program (Kids First) is a trans-NIH effort initiated in response to the 2014 Gabriella Miller Kids First Research Act and supported by the NIH Common Fund. This program focuses on gene discovery in pediatric cancers and structural birth defects and the development of the Gabriella Miller Kids First Pediatric Data Resource (Kids First Data Resource). All of the genomic and phenotypic data from this study are accessible through dbGaP. The data is also available at the Kids First Portal, where other Kids First datasets can also be accessed in the cloud for data analysis, data visualization, collaboration and interoperability, open to all researchers and developers.

Microtia is a rare congenital deformity of the external ear, the pinna. The severity of microtia is variable and ranges from subtle deformities in the pinna to absence of the external ear. Microtia is often associated with closure of the external auditory ear canal causing significant hearing loss. Microtia can be an isolated, unilateral or bilateral malformation, or occur solely with ear canal deformities, or with additional craniofacial or syndromic manifestations. Earlier studies of identical twins with microtia demonstrated a significant genetic contribution. The molecular pathogenesis for most microtia remains unknown. We propose to leverage our clinical acumen in diagnosis and treatment of microtia (R.E.), our relationship to the microtia community (M.T.) and our collected DNA samples from microtia patients to identify genetic variant(s) that contribute to this congenital malformation. Microtia prevalence is much higher among Native Americans and some Latin Americans (17 per 10,000 Ecuadorian births) than among individuals of European-descent (0.6 - 1.6 per 10,000 births). To capitalize on this epidemiologic data, we have recruited microtia cohorts from Latin America and the U.S, including clinical data and DNA samples.
Apply for Access on dbGaP

Studies Page on the Kids First Portal

dbGaP Access Page - Request Access
Apply for Access on dbGaP

File Repository on the Kids First Portal

dbGaP Access Page - Request Access
Apply for Access on dbGaP

Kids First Studies and Access Page

dbGaP Access Page - Request Access
Clinical Data Review for Kids First Projects

Part of the collaboration between the Kids First DRC and our Investigators.

Looking for...

- Is all clinical data from the original X01 application included?
- Does the list of samples on the sequencing manifest match the samples in the clinical data?
- Do all fields contain accepted values?
- Is data consistent across multiple fields?

Some studies require several rounds of revision to reach a state where NIH will approve the data for delivery and release.
Bioinformatics Resources - Harmonized Genomics Files

Genomic Samples
- Aligned genomes (.cram)
- Called germline variants (.gVCFs)

Trio-Based Studies
- Family-based joint-called variants (.VCFs)

Tumor-Normal Studies
- Annotated Somatic Variants (.VCFs and .MAFs)
  - SNVs
  - CNVs
  - SVs

RNA-Sequencing Studies
- Unaligned reads (.fastq)
- Aligned reads (.cram)
- Expression counts (.tsv)

**harmonized**: all run through the same workflow, allowing for cross-disease comparisons and analyses
Bioinformatics Resources - Pipelines & Workflows

Alignment & GATK HaplotypeCaller
Trio-Based Joint Genotyping
Somatic Variants (Tumor-Normal)
RNA-Sequencing

Bring your own data!

Available on CAVATICA and GitHub for use.
Receive Cloud Credits to Support Your Research!

NIH is sponsoring a **cloud credits program** to support projects on CAVATICA.

Receive allocated credits for...

- Research projects using Kids First datasets
- Developing software tools to analyze Kids First datasets

**Web:** [https://github.com/kids-first/kf-cloud-credits](https://github.com/kids-first/kf-cloud-credits)

**Email:** KidsFirst@od.nih.gov
Kids First Office Hours - Monthly Help Sessions

Monthly User Support Office Hours

Next Session:
Tuesday, October 11
3:00pm to 4:00pm/ET

To Join, Follow the Link:
tinyurl.com/KidsFirstOfficeHours

Questions? Contact:
higginsd@chop.edu