OSC (Common Fund)

The Common Fund

Concept Clearance:

The Gabriella Miller Kids First Pediatric Research Program (Phase 2)

Objectives:

1. Additional generation of childhood cancer and structural birth defects-related omics data
2. Continue development and improvement of the Data Resource
3. Expert-driven activities to increase the value of Kids First data

Funds Available: $12,600,000 per year

Program Duration: 3 years

Council Action: Vote on support for Stage 2 of the Gabriella Miller Kids First Pediatric Research Program

Gabriella Miller Kids First Pediatric Research Program: Plans for FY22-24

How did Kids First get started?

At 9 years old, Gabriella Miller was diagnosed with DIPG – Diffuse Intrinsic Pontine Glioma – an inoperable brain tumor and became a vocal advocate for pediatric research. She passed away less than a year after diagnosis, six months before the **2014 Gabriella Miller Kids First Research Act** was signed.

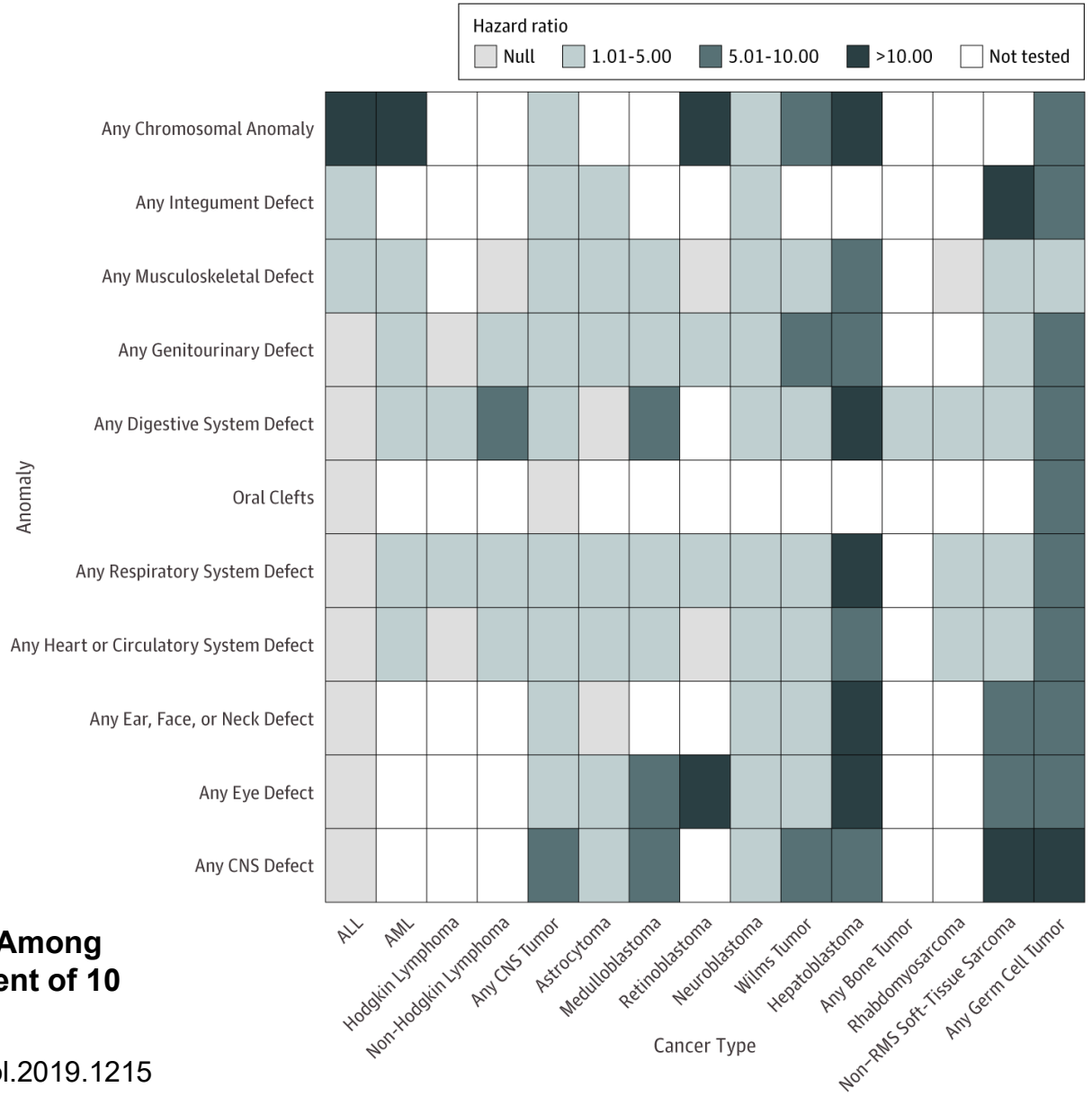
- Signed into law on April 3, 2014
- Ended taxpayer contribution to presidential nominating conventions
- Transferred $126 million into the Pediatric Research Initiative Fund
- Authorized $12.6 million per year for 10 years to the NIH Common Fund
- To fund grants for pediatric research; first appropriation was for FY2015

Vision

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.

Why study childhood cancer & structural birth defects together?

- ***Both are leading causes of mortality in childhood***
- ***Birth defects are associated with increased risk of cancer among children… suggesting shared genetic pathways***



From: **Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births**

Lupo et al, JAMA Oncol. 2019;5(8):1150-1158. doi:10.1001/jamaoncol.2019.1215

Kids First Major Initiatives

Through 2021:

1. Identify & sequence cohorts of children with **childhood cancer and/or structural birth defects**.
2. Build the **Gabriella Miller Kids First Data Resource** to empower discovery

Year	15 ✓	16 ✓	17 ✓	18 ✓	19 ✓	20	21	22	23	24

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM Data Resource Center

Phase 2

Kids First Sequencing Cohorts 2015-2019

39 projects | 37,000 WGS | 15,000 cases | 13 released datasets | >150 Data Access Requests

BROAD INSTITUTE | HUDSONALPHA INSTITUTE FOR BIOTECHNOLOGY | St. Jude Children's Research Hospital

- Congenital Diaphragmatic Hernia
- Disorders of Sex Development
- Ewing Sarcoma
- Structural Heart & Other Defects
- Syndromic Cranial Dysinnervation Disorders
- Cancer Susceptibility
- Adolescent Idiopathic Scoliosis
- Neuroblastomas
- Enchondromatoses
- Orofacial Clefts in Caucasian, Latin American, Asian & African, Filipino populations
- Osteosarcoma
- Familial Leukemia
- Craniofacial Microsomia
- Hemangiomas, Vascular Anomalies & Overgrowth
- Nonsyndromic Craniosynostosis
- Patients with both childhood cancer and birth defects
- Kidney and Urinary Tract Defects
- Microtia
- Hearing Loss
- Bladder Exstrophy
- Cornelia de Lange Syndrome
- Intracranial & Extracranial Germ Cell Tumors
- Esophageal Atresia and Tracheoesophageal Fistulas
- Fetal Alcohol Spectrum Disorders
- Myeloid Malignancies + overlap with Down syndrome
- Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome
- Structural Brain Defects
- Structural Defects of the Neural Tube (Spina Bifida: Myelomeningocele)
- CHARGE Syndrome
- Laterality Birth Defects
- T-cell Acute Lymphoblastic Leukemia
- Pediatric Rhabdomyosarcoma

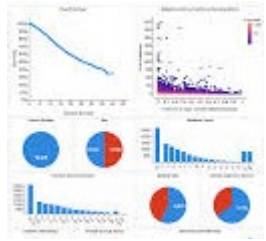
The Kids First Data Resource for Collaborative Discovery

Data Resource Portal

Entry point. Query, search, discover, build & visualize synthetic cohorts

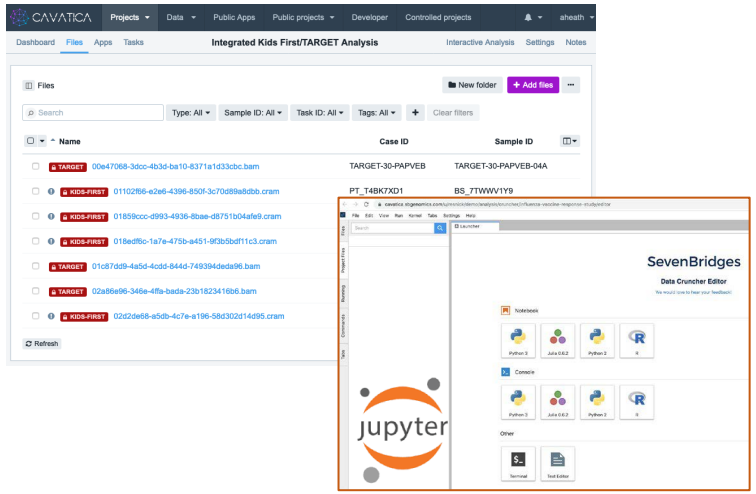
Knowledge Base Integrations (PedcBioPortal)

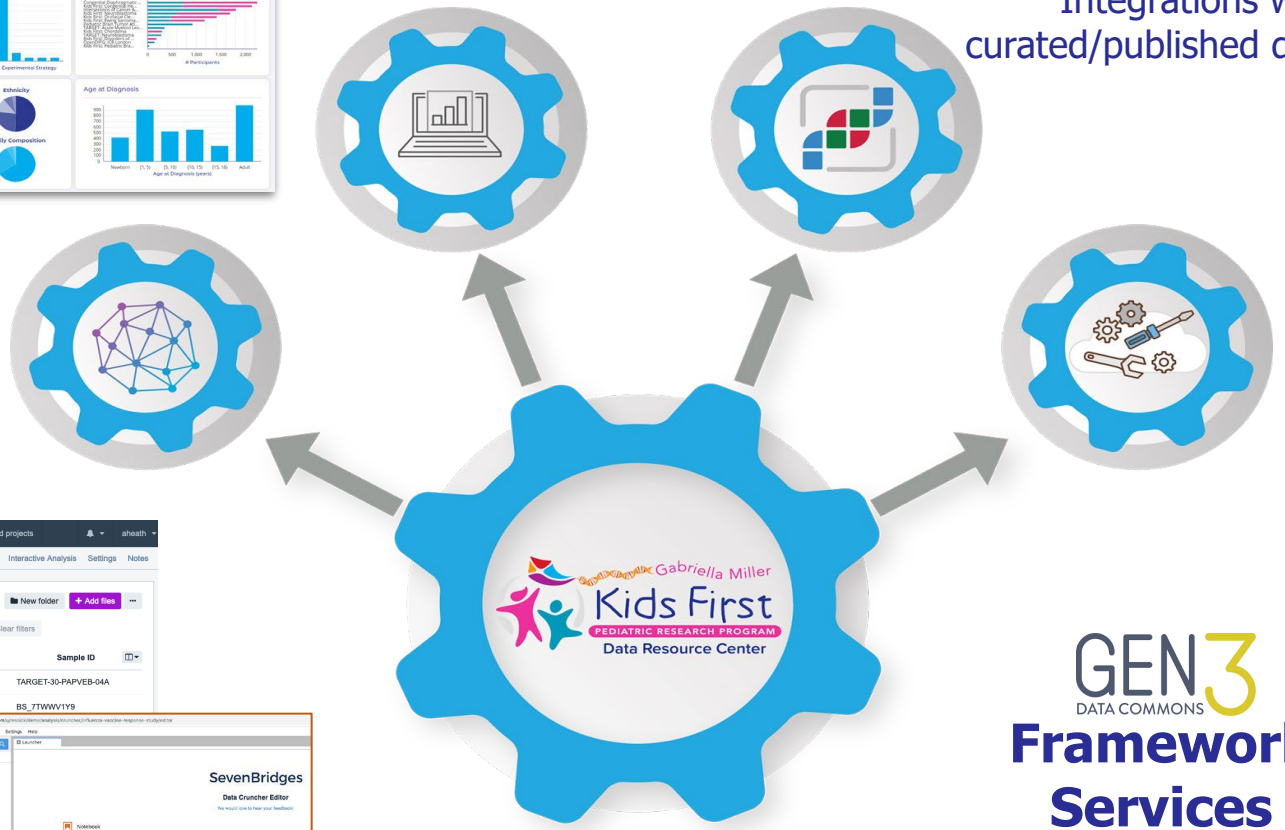
Integrations with existing curated/published data visualizations



Cavatica

Pull data from multiple sources into one workspace.
Use notebooks, bring-your-own or use available workflows.





Data Services

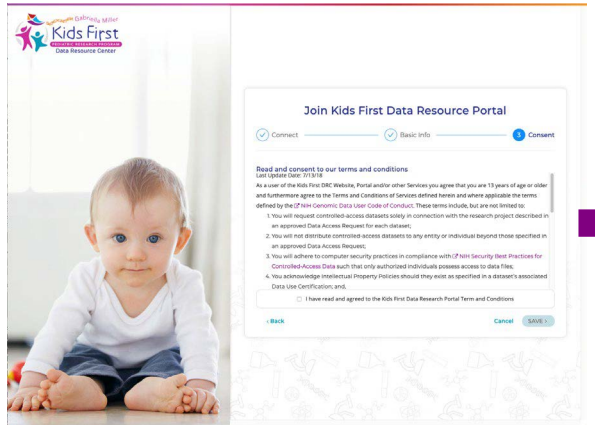
Model clinical data in FHIR-based data services for semantic interoperability and coordination

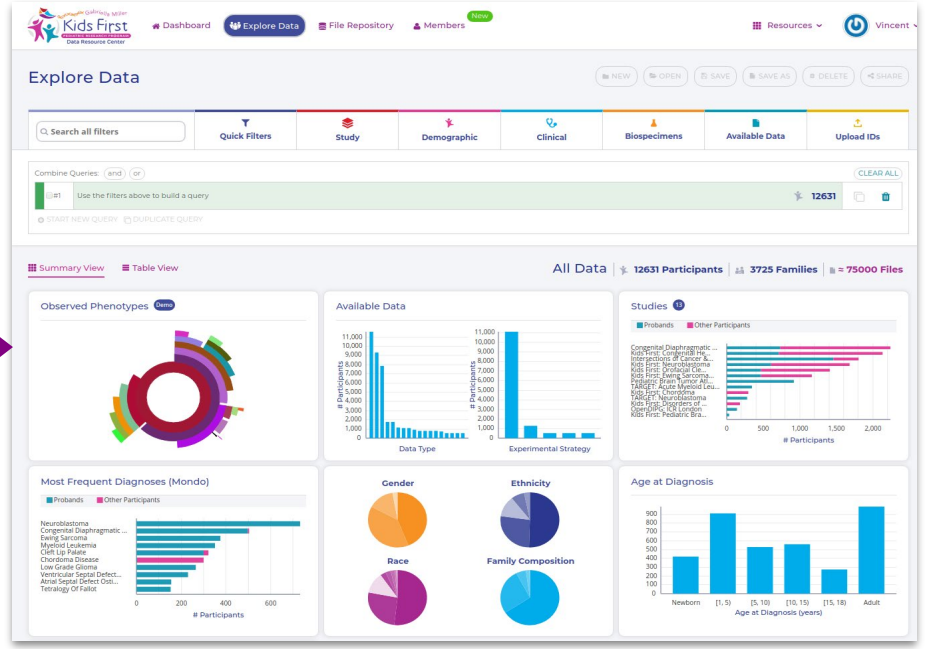
GEN3 DATA COMMONS Framework Services

Index and point to files in the cloud (for approved users)

Data Resource Use Case: Compare genetic variants of congenital heart defects & neuroblastoma

Anyone can register & login to the portal (via ORCHID, Google). User agrees to terms

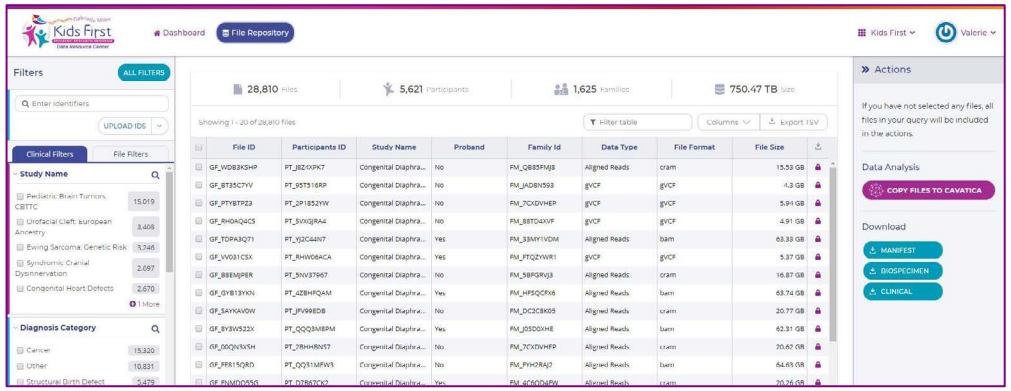




In *Explore Data*, user searches the terms "heart" and "neuroblastoma". Discovers data from children with congenital heart disease (KF & BDC data) & neuroblastoma (KF & NCI TARGET)

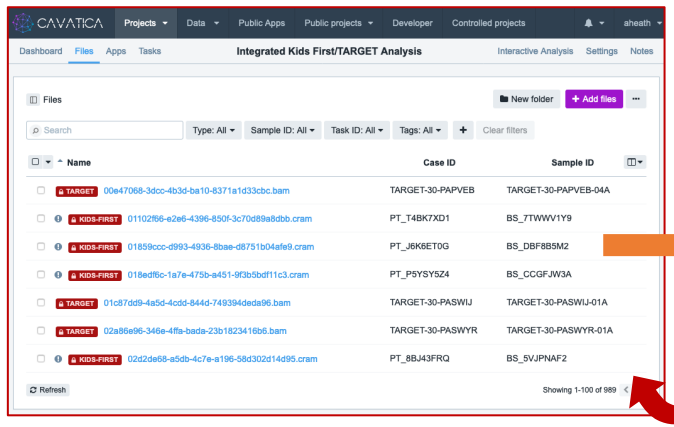
User builds a synthetic cohort based on these criteria and can view summary & deidentified individual-level clinical, demographic, and phenotypic information.

Synthetic cohort is ported to the *File Repository* where user selects which **genomic** and **histology image** files they want to analyze.

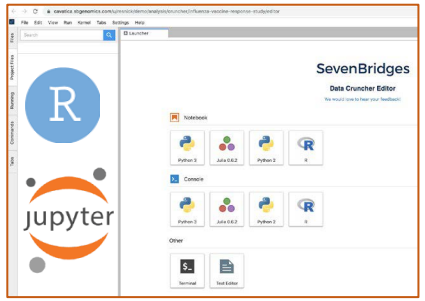


User has or applies for dbGaP access for genomic data

User pushes genomic, clinical data, and image data into Cavatica for analysis & visualization



User runs statistical analysis in notebooks



User iterates through genomic workflows

Impact: Researchers Are Making Discoveries

17 Journal Publications To-Date

ELSEVIER
Guide for Authors | About | Explore this Journal
AJHG

Am J Hum Genet. 2019 Sep 5; 105(3): 658–668.
Published online 2019 Aug 29. doi: 10.1016/j.ajhg.2019.07.020
PMCID: P
PMI

Germline 16p11.2 Microdeletion Predisposes to Neuroblastoma

Laura E. Egolf,[1,2,3] Zalman Vaksman,[2,3,4] Gonzalo Lopez,[2,3,4] Jo Lynne Rokita,[2,3,4] Apexa Modi,[2,3] Patricia V. Basta,[6,7] Hakon Hakonarson,[8,9] Andrew F. Olshan,[6,7] and Sharon J. Diskin[1,2,3,4,5,10,*]

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nature genetics
ARTICLES
https://doi.org/10.1038/s41588-020-0652-z
Check for updates

Genomic analyses implicate noncoding de novo variants in congenital heart disease

Felix Richter[1,31], Sarah U. Morton[2,3,31], Seong Won Kim[4,31], Alexander Kitaygorodsky[5,31], Lauren K. Wasson[4,31], Kathleen M. Chen[6,31], Jian Zhou[6,7,8], Hongjian Qi[5], Nihir Patel[9], Steven R. DePalma[4], Michael Parfenov[4], Jason Homsy[4,10], Joshua M. Gorham[4], Kathryn B. Manheimer[1,11], Matthew Velinder[12], Andrew Farrell[12], Gabor Marth[12], Eric E. Schadt[9,11,13], Jonathan R. Kaltman[14], Jane W. Newburger[15], Alessandro Giardini[16], Elizabeth Goldmuntz[17,18], Martina Brueckner[19], Richard Kim[20], George A. Porter Jr.[21], Daniel Bernstein[22], Wendy K. Chung[23], Deepak Srivastava[24,32], Martin Tristani-Firouzi[25,32], Olga G. Troyanskaya[6,7,26,32], Diane E. Dickel[27,32], Yufeng Shen[5,32], Jonathan G. Seidman[4,32], Christine E. Seidman[4,28,32] and Bruce D. Gelb[9,29,30,32]

Human Mutation
Variation, Informatics, and Disease
OFFICIAL JOURNAL HGV HUMAN GENOME VARIATION SOCIETY

RESEARCH ARTICLE | Full Access

Deleterious de novo variants of X-linked *ZC4H2* in females cause a variable phenotype with neurogenic arthrogryposis multiplex congenita

Suzanna G.M. Frints, Friederike Hennig, Roberto Colombo, Sebastien Jacquemont, Paulien Terhal, Holly H. Zimmerman, David Hunt, Bryce A. Mendelsohn, Ulrike Kordaß ... See all authors

First published:17 June 2019 | https://doi.org/10.1002/humu.23841

Springer Link

Original Investigation | Open Access | Published: 17 December 2019

Whole genome sequencing of orofacial cleft trios from the Gabriella Miller Kids First Pediatric Research Consortium identifies a new locus on chromosome 21

Nandita Mukhopadhyay, Madison Bishop, Michael Mortillo, Pankaj Chopra, Jacqueline B. Hetmanski, Margaret A. Taub, Lina M. Moreno, Luz Consuelo Valencia-Ramirez, Claudia Restrepo, George L. Wehby, Jacqueline T. Hecht, Frederic Deleyiannis, Azeez Butali, Seth M. Weinberg, Terri H. Beaty, Jeffrey C. Murray, Elizabeth J. Leslie, Eleanor Feingold & Mary L. Marazita

Human Genetics **139**, 215–226(2020) | Cite this article

PLOS GENETICS

OPEN ACCESS PEER-REVIEWED
RESEARCH ARTICLE

De novo variants in congenital diaphragmatic hernia identify *MYRF* as a new syndrome and reveal genetic overlaps with other developmental disorders

Hongjian Qi, Lan Yu, Xueya Zhou, Julia Wynn, Haoquan Zhao, Yicheng Guo, Na Zhu, Alexander Kitaygorodsky, Rebecca Hernan, Gudrun Aspelund, Foong-Yen Lim, Timothy Crombleholme, Robert Cusick, [...], Yufeng Shen [view all]

Version 2 ▾ Published: December 10, 2018 • https://doi.org/10.1371/journal.pgen.1007822

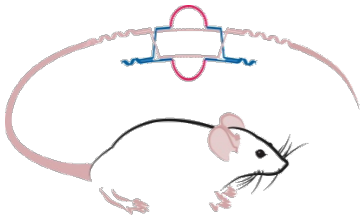
Collaborations amplify the impact of Kids First

COMMON FUND DATA ECOSYSTEM

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

db GaP GENOTYPES and PHENOTYPES

BioData CATALYST



IMPC International Mouse Phenotyping Consortium

KOMP2

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

AnVILproject

STRIDES aws

Cloud Credits Pilot

NIH NATIONAL CANCER INSTITUTE Cancer Research Data Commons

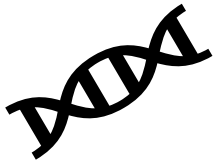
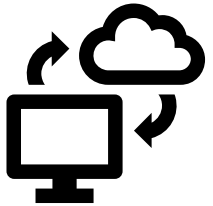
What is next for Kids First?

2018 Strategic (Re-)Planning Exercise:

- **2018 Program Survey launched at ASHG:** Kids First & external investigators
- **Kids First Steering Committee**
- **External Program Consultants**
- **DRC Admin & Outreach Core** (feedback from the public, patients, foundations)
- **NIH Kids First Working Group & Co-Chairs**

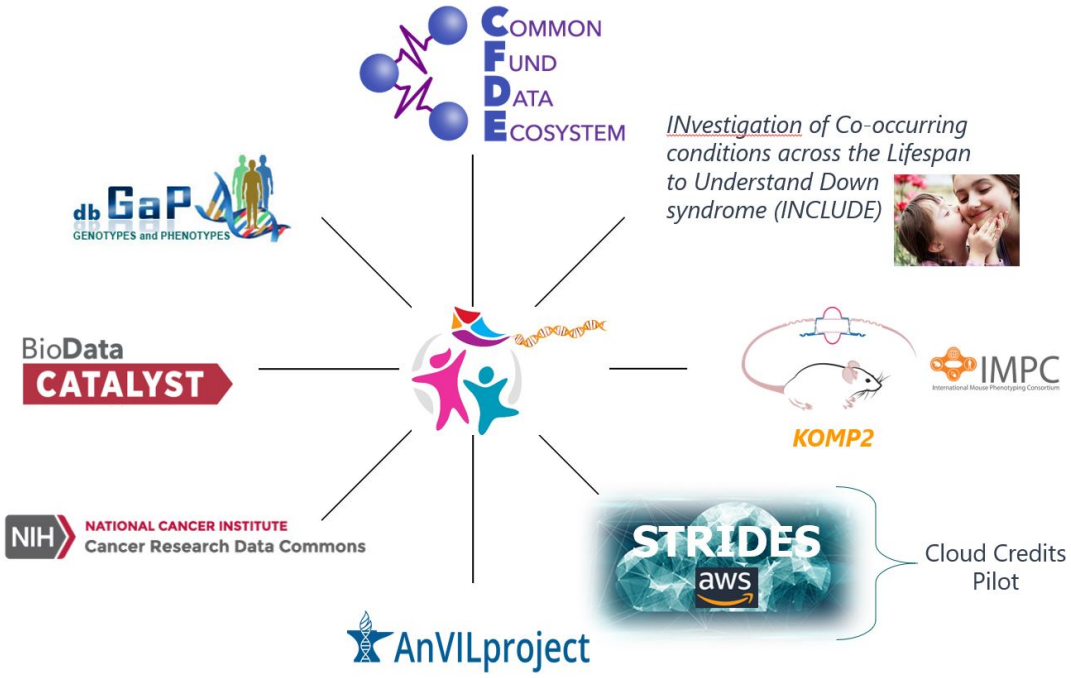
Proposed Phase 2: $12.6M/year (FY22-24)

1) **Additional generation of childhood cancer and structural birth defects-related -omics data**
   - ➢Add epigenomic and proteomic assays
2) **Continue development & improvement of the Data Resource**
   - ➢Plan for sustaining the Data Resource beyond FY24
3) **Expert-driven activities to increase the value of Kids First data**
   - ➢Engage Kids First & community experts in activities such as integration, curation, and/or harmonization of rich clinical and phenotypic data

In Parallel, Continue Trans-NIH Collaborations

- **Interoperability with other NIH efforts**
  - NCPI activities and ODSS collaborations
  - The Common Fund Data Ecosystem
  - New interoperability opportunities with a focus toward federating NIH-wide pediatric data



- **Draw more researchers to the cloud**
  - Continue STRIDES Cloud Credit Distribution Pilot with Kids First investigators and consider opening to the wider research community
- **Continue IC-led complementary support for research discoveries**
  - Analysis grants: NICHD-led R03, NIDCR R03s, & R01s
  - Model organism functional genomics

Acknowledgments

Kids First Working Group

Eunice Kennedy Shriver National Institute of Child Health and Human Development (**NICHD**)

National Human Genome Research Institute (**NHGRI**)

National Heart, Lung, and Blood Institute (**NHLBI**)

National Cancer Institute (**NCI**)

Other Working Group Representation:

NIDCR	**NIAAA**	**NIDDK**	**NEI**	**NIAID**	**ORIP**
NIDA	**NINDS**	**NIEHS**	**NIAMS**	**NCATS**	**CDC**

Kids First DRC

D3b Center for Data-Driven Discovery in Biomedicine

Children's Hospital of Philadelphia℠

SevenBridges genomics

OICR Ontario Institute for Cancer Research | IORC Institut ontarien de recherche sur le cancer

THE UNIVERSITY OF CHICAGO

OHSU OREGON HEALTH & SCIENCE UNIVERSITY

Children's National Health System

Thank You!