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
**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.
Kids First Sequencing Cohorts 2015-2019

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

- 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 Microsoma
- 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 & Excranial 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

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

Knowledge Base Integrations (PedcBioPortal)
Integrations with existing curated/published data visualizations

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

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

User has or applies for dbGaP access for genomic data.

User runs statistical analysis in notebooks.

User iterates through genomic workflows.
Impact: Researchers Are Making Discoveries

17 Journal Publications To-Date

Genomic analyses implicate noncoding de novo variants in congenital heart disease


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

Suzanna G.M. Frants, Frederike Henning, Roberto Colombo, Sebastien Jacquemont, Paulien Terhal, Holly H. Zimmerman, David Hunt, Bryce A. Mendlebohn, Ullrike Noccioli

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

Sandra Nakazawab, Madison Bishop, Michael Marcilla, Rebecca Chaves, Jacqueline R. Hietamaki, Margaret A. Taib, Lisa M. Moreno, Leo Contraste, Valencia Ramirez, Claudia Epstean, George L. Wetherby, Jacqueline T. Hirsch, Frederik DeLange, Anees Batal, Seth M. Weinberg, Tom J. Batty, Jeffrey C. Murray, Elizabeth A. Leslie, Elanor Feingold, and Mary L. Manley

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

Hongan Gao, Lan Yu, Xiaoya Zhou, Julia Wym, Haoguan Zhao, Yichang Guo, Na Zhu, Alexander Kitaygorodsky, Rebecca Hansen, Gudrun Aspelund, Fang-Ying Liu, Timothy Combsaton, Robert Conick, and Yufeng Shen
Collaborations amplify the impact of Kids First

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

NIH Cloud-Based Platforms Interoperability (NCPI): Empower end-user analyses across platforms through federation & interoperability
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
  o NCPI activities and ODSS collaborations
  o The Common Fund Data Ecosystem
  o New interoperability opportunities with a focus toward federating NIH-wide pediatric data

• Draw more researchers to the cloud
  o 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
- Seven Bridges Genomics
- OICR
- The University of Chicago
- OHSU
- Children's National Health System
Thank You!