Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

Spring Webinar

Empowering Discovery through a Wide Variety of Data Types

May 11, 2022
2-4 pm ET

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Webinar Agenda

2:00 pm – Collaborate to Accelerate Discoveries in Pediatric Research
Host: Dr. Marcia Fournier, NIH Kids First Program Manager

2:15 pm – Keynote: Cancer Risk in Children with Birth Defects: How Kids First Can Move Observation into Understanding
Keynote Speaker: Dr. Philip Lupo, Kids First Investigator

2:45 pm – Kids First Variant Search Tool: Exploring Datasets to Jump Start Analyses
Guest Speakers: Dr. Adam Resnick & Dr. David Higgins, Kids First Data Resource Center

3:15 pm – Kids First Cloud Credits Pilot Announcement
Guest Speaker: Valerie Cotton, NIH NICHD

3:30 pm – Relevant NIH Mechanisms to Support Research Using Kids First Data & Resources
Guest Speaker: Dr. James Coulombe, NICHD

3:45 pm – Q&A

Marcia Fournier, PhD

Program Manager

Gabriella Miller Kids First Pediatric Research Program

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Marcia Fournier

@MarciaFournier2

Collaborate to Accelerate Discoveries in Pediatric Research

Introduction about Kids First Program

Pediatric Cancer Awareness and Scientific Hypothesis Brought the Kids First Program Together

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

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

Scientific Hypothesis: Intersection of Cancer and Pediatric Conditions

Sept 2012
First Birth Defect and Cancer Workshop by NIH

Shared mutations:
BRAF
MAPK
ALK

The New York Times

Birth Defects Tied to Higher Cancer Risk

Major birth defects are associated with an increased risk for cancer in childhood. New research suggests the risk persists into adulthood.

Give this article | 3

By Nicholas Bakalar

Dec. 7, 2020

Original Investigation | FREE

June 20, 2019

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

Philip J. Lupo, PhD[1,2]; Jeremy M. Schraw, PhD[3]; Tania A. Desrosiers, PhD[4]; et al

» Author Affiliations | Article Information

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

RESEARCH

BMJ 2020;371:m4060 | doi: 10.1136/bmj.m4060

Cancer risk in individuals with major birth defects: large Nordic population based case-control study among children, adolescents, and adults

Dagrun Slettebø Daltveit,[1] Kari Klungsøyr,[1,2] Anders Engeland,[1,2] Anders Ekbom,[3] Mika Gissler,[4,5] Ingrid Glimelius,[6,7] Tom Grotmol,[8] Laura Madanat-Harjuoja,[9,10] Anne Gulbech Ording,[11] Solbjørg Makalani Myrtveit Sæther,[12] Henrik Toft Sørensen,[11] Rebecca Troisi,[13] Tone Bjørge[1,8]

Who is Behind the Kids First Program

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**)

NIH The Common Fund

Other Working Group Representation:

NIDCR **NIAAA** **NIDDK** **NEI** **NIAID** **ORIP**

NIDA **NINDS** **NIEHS** **NIAMS** **NCATS** **CDC**

The **Gabriella Miller Kids First Pediatric Research** is a trans-NIH initiative that enables researchers, clinicians, and patients to work together to **accelerate collaborative research and promote new discoveries** for children affected with cancer and structural birth defects

Kids First Program Addresses Genomic Studies for Pediatric Cancer and Structural Birth Defects

- **Grow a data resource in the cloud** to accelerate pediatric cancer and structural birth defects research leading to better prevention, diagnosis, and treatments for patients and families
  - FAIR Data
  - Data sharing
  - Data analysis and visualization
  - Collaborative research

What Differentiates the Kids First Data & Resources

- Program offers opportunity of whole genome sequencing
- Public data available with phenotypes and clinical data
- Multiple pediatric conditions and childhood cancer
  - Commonalities/ differences between phenotypes
  - Trios – patients and families
  - Variant call

How Kids First Program Supports Research

Research Program Empowered by Sequencing Centers and Data Resource Center

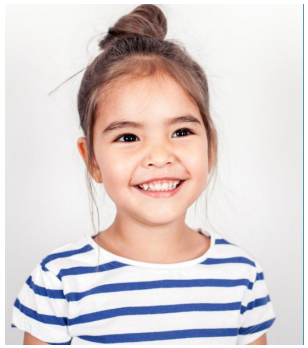
X01

PAR-22-054, 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)

1. Selected investigators send DNA/ RNA samples to Sequence Centers
2. Sequencing Centers generate genomic data with investigators' samples
3. Data Resource Center
   - Compile sequencing with phenotypes and clinical data provided by investigators
   - Release data to investigators
   - Investigators have exclusivity of the data for 6-months

Kids First Accelerates Research Through Data Sharing

- Harmonized data, tools, and resources in the cloud
- Almost 3,000 registered users since 2018 launch



Quick Start

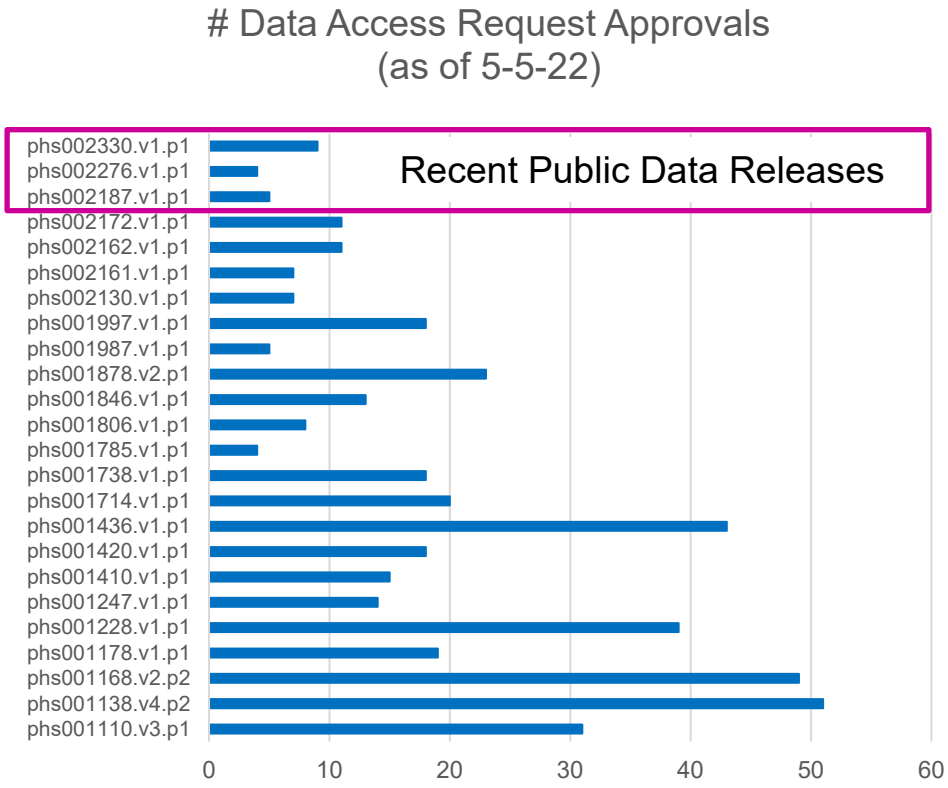
1. Join the Kids First Portal or Log In and fill out your user profile.
2. Go to your settings page to connect your account to GEN3 and CAVATICA to perform analysis.
3. Browse the data in the File Repository, performing queries based on your research interests.

30	27,800	25,421	82,104	131,701	1.52 PB
Studies	Participants	Families	Samples	Files	Size

Kids First Data Sharing Fast Growing

Approx. 20% growth in Kids First data access since Fall 2021

1. 56 sequencing projects
2. 28 Publications
3. 24 studies at dbGaP
4. 442 data access requests approved to date



Kids First Data Release since Fall 2021

- Almost 4000 new subjects

Kids First: Myeloid Malignancies 408 subjects

First Portal Releas...	September 23, 2021
Data Types Availa...	Aligned Reads, Individual gVCFs, Family-Based VCFs
Sequencing Center	HudsonAlpha Institute with additional harmonized data generated by the DRC
About the Study	NIH X01 Project Abstract - Soheil Meshinchi, PI

Kids First: T-Cell ALL 1327 subjects

First Portal Releas...	November 1, 2021
Data Types Availa...	Aligned Reads, VCFs
Sequencing Center	HudsonAlpha Institute with additional harmonized data generated by the DRC
About the Study	NIH X01 Project Abstract - David Teachey, PI

Kids First: Leukemia & Heart Defects in Down Syndrome 2067 subjects

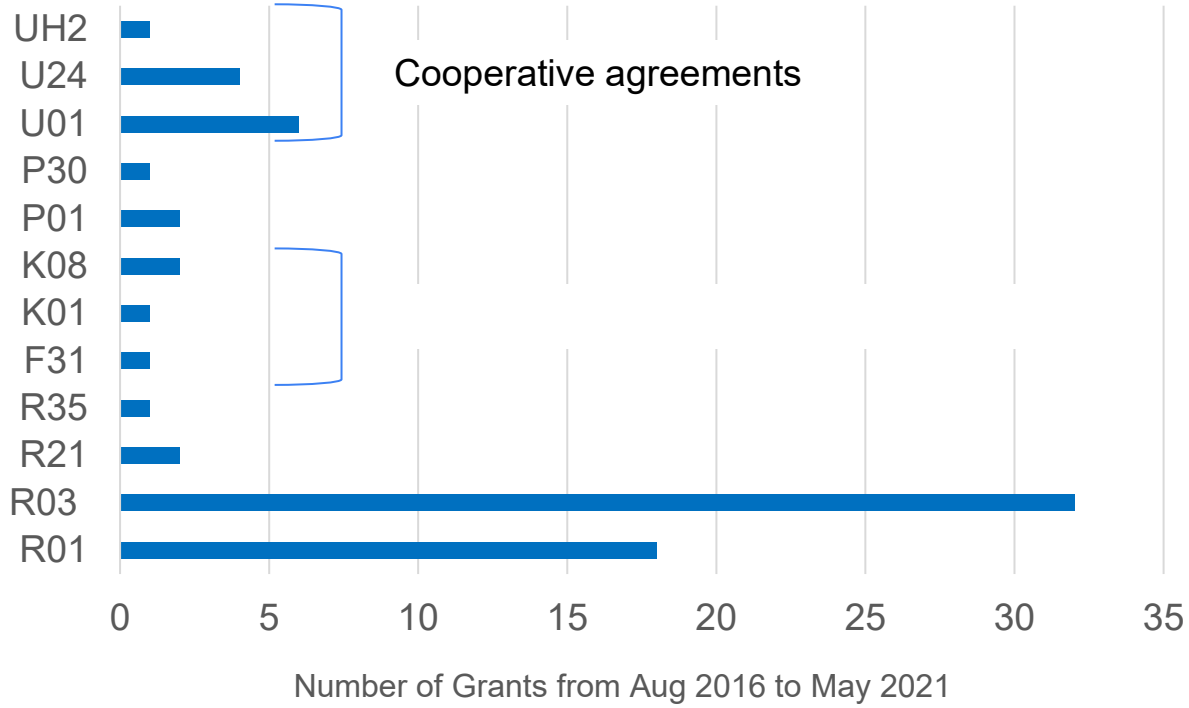
First Portal Releas...	September 28, 2021
Data Types Availa...	Aligned Reads, Individual gVCFs, Family-Based VCFs
Sequencing Center	Broad Institute with additional harmonized data generated by the DRC
About the Study	NIH X01 Project Abstract - Philip Lupo and Stephanie Sherman, PIs

NIH Support Mechanisms for Kids First Data Analysis

- **RO3**
  - RFA-RM-22-006, Expert-Driven Small Projects to Strengthen Gabriella Miller Kids First Discovery (R03 Clinical Trial Not Allowed) – Due date June 10!
  - PAR-19-375, Small Research Grants for Analyses of Gabriella Miller Kids First Pediatric Research Data (R03 Clinical Trial Not Allowed)
  - PAR-20-060, Small Research Grants for Establishing Basic Science-Clinical Collaborations to Understand Structural Birth Defects (R03 Clinical Trial Not Allowed)
- **R01**
  - PAR-20-137, In-Depth Phenotyping and Research Using IMPC-Generated Knockout Mouse Strains Exhibiting Embryonic or Perinatal Lethality or Sub viability (R01 Clinical Trial Not Allowed).
  - PAR-21-229, Screening and Functional Validation of Human Birth Defects Genomic Variants (R01 Clinical Trial Not Allowed)

Kids First Data is Enabling Research

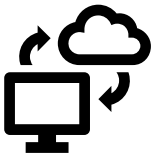
- Over 70 NIH Research Grants Using Kids First Data & Resources



Future with Multiple Data Types, Collaboration and Interoperability

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

- Additional generation of childhood cancer and structural birth defects-related -omics data
  - Add multiple data types such as epigenomic and proteomic
  - Add longitudinal data, data enrichment with phenotypes, clinical data, and outcomes
- Continue development & improvement of the Data Resource
  - Enable discovery and data generation
  - Cross diseases collaborations
  - Interoperability
- 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



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

Philip Lupo, PhD, MPH

Epidemiologist and
Professor of Pediatrics

Baylor College of Medicine

Philip Lupo @plupo1

Keynote

Cancer Risk in Children with Birth Defects: How Kids First Can Move Observation into Understanding

Cancer Risk in Children with Birth Defects: How Kids First Can Move Observation into Understanding

Philip Lupo, PhD, MPH
Department of Pediatrics
Section of Hematology-Oncology
Baylor College of Medicine

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

Baylor College of Medicine

Texas Children's Cancer Center

Outline

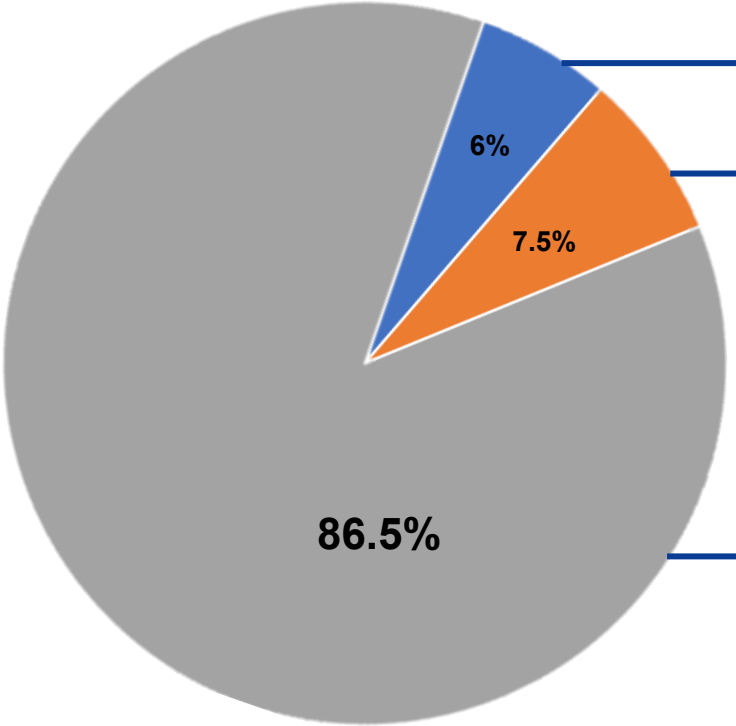
- **Cancer risk in children with birth defects**: observations from registry-based studies
- **Building from Kids First to discover novel congenital anomaly-cancer syndromes**: Genetic Overlap Between and Anomalies and Cancer in Kids (GOBACK) Study
- **Leveraging Kids First to identify children with congenital anomalies who are more likely to develop cancer**: Down syndrome-acute lymphoblastic leukemia

Gabriella Miller Kids First ATRIC RESEARCH PROGRAM

Baylor College of Medicine

Texas Children's Cancer Center

Birth defects and cancer risk



Chromosomal anomalies
Example: Trisomy 21 and acute lymphoblastic leukemia

Single gene defects
Example: Costello syndrome and rhabdomyosarcoma

Non-syndromic birth defects
Multifactorial; cancer risk largely unknown

March of Dimes; Taub JW, *J Pediatr Hematol Oncol*. 2001; Genetics Home Reference

(Some) research questions and the role of Kids First

1. Which birth defects are associated with which cancers?
2. Do specific birth defect-cancer associations represent undiscovered Mendelian syndromes?
3. Why do some children with birth defects develop cancer while others do not?

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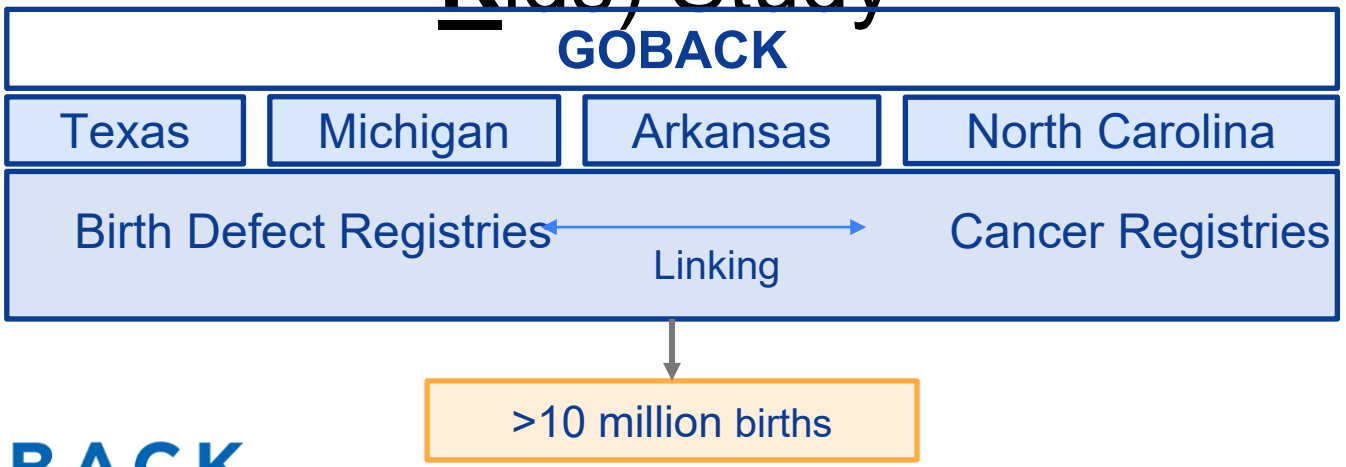
Baylor College of Medicine

Texas Children's Cancer Center

GOBACK (**G**enetic **O**verlap **B**etween **A**nomalies and **C**ancer in **K**ids) Study



GOBACK
TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids

GOBACK registry linkage cohort

Unaffected children

N ≈ 9.6M

Children with cancer but no birth defect

N ≈ 15,000

Children with a birth defect who do not develop cancer

N ≈ 524,000

Children with both birth defects and cancer

N ≈ 2,100

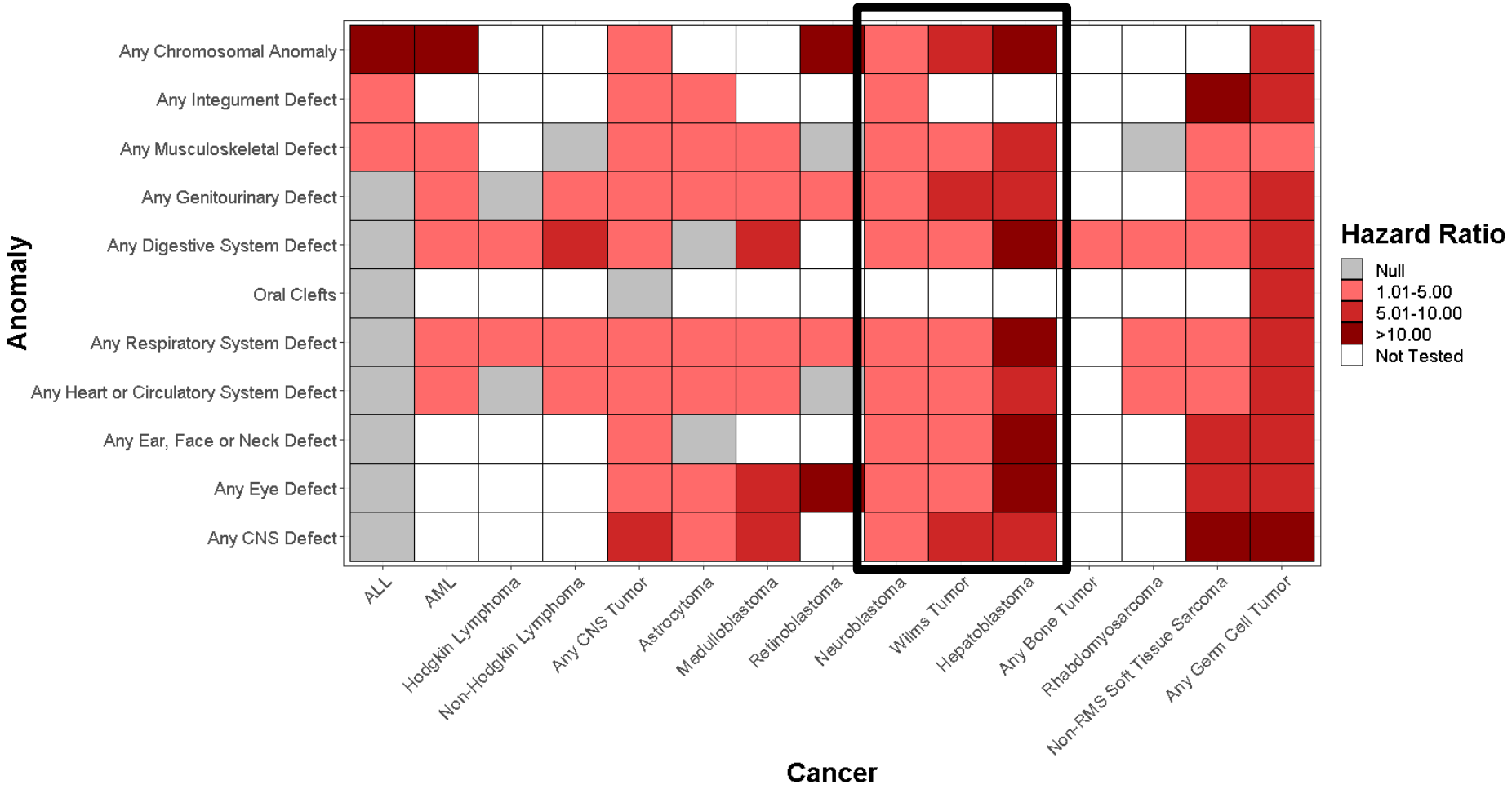
Jeremy Schraw, PhD

JAMA Oncol. 2019 Jun 20;5(8):1150-8

Risk of any cancer in children with birth defects

Birth Defect	Cancer	N Comorbid	HR (95% CI)
Any non-chromosomal birth defect	Any childhood cancer	1,740	2.6 (2.4-2.7)
Any chromosomal birth defect	Any childhood cancer	383	11.6 (10.4-12.9)

JAMA Oncol. 2019 Jun 20;5(8):1150-8


Anomaly
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Any Integument Defect
Any Musculoskeletal Defect
Any Genitourinary Defect
Any Digestive System Defect
Oral Clefts
Any Respiratory System Defect
Any Heart or Circulatory System Defect
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Any Eye Defect
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Any CNS Tumor
Astrocytoma
Medulloblastoma
Retinoblastoma
Neuroblastoma
Wilms Tumor
Hepatoblastoma
Any Bone Tumor
Rhabdomyosarcoma
Non-RMS Soft Tissue Sarcoma
Any Germ Cell Tumor
Cancer
Hazard Ratio
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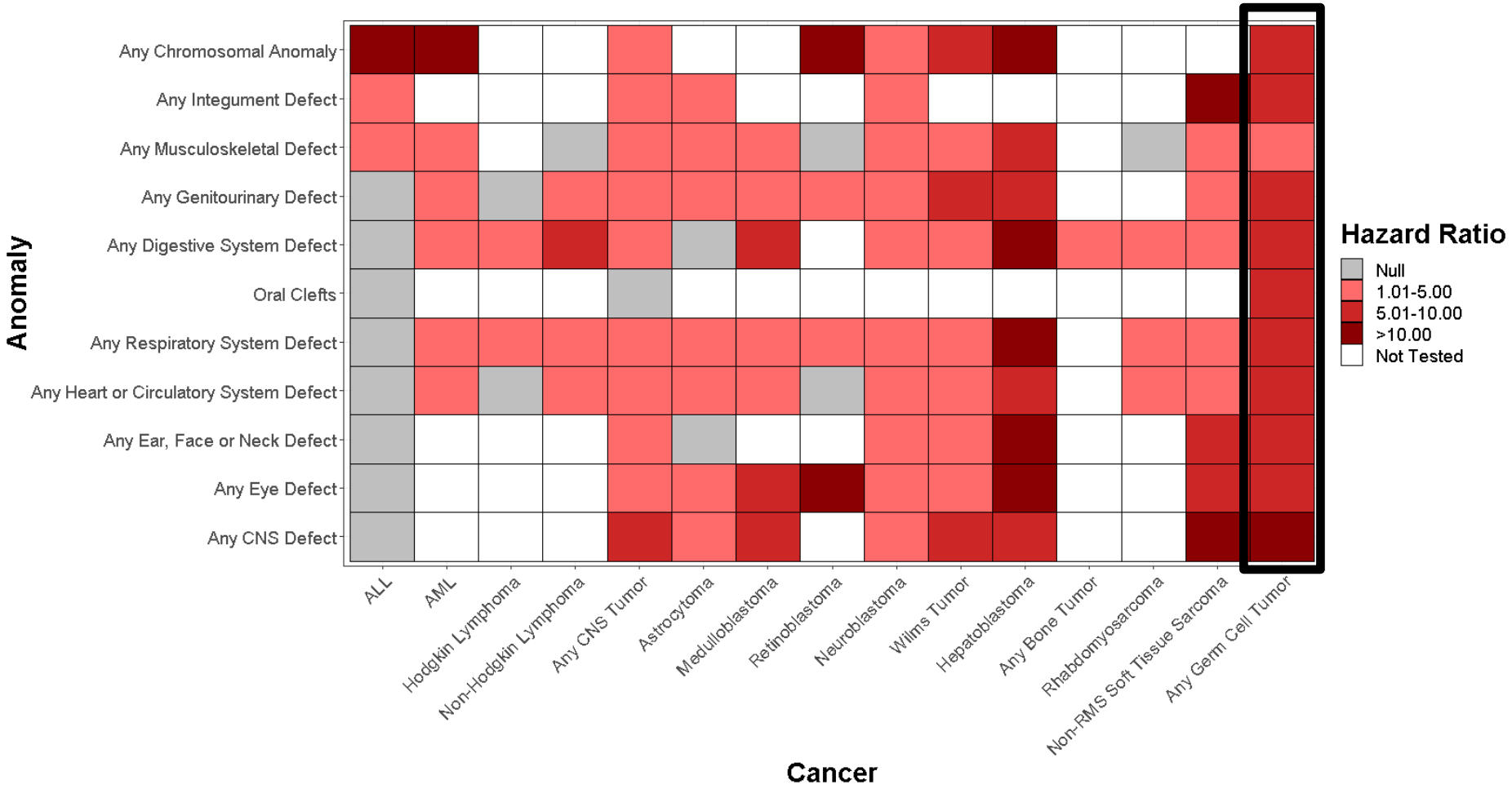
1.01-5.00
5.01-10.00
>10.00
Not Tested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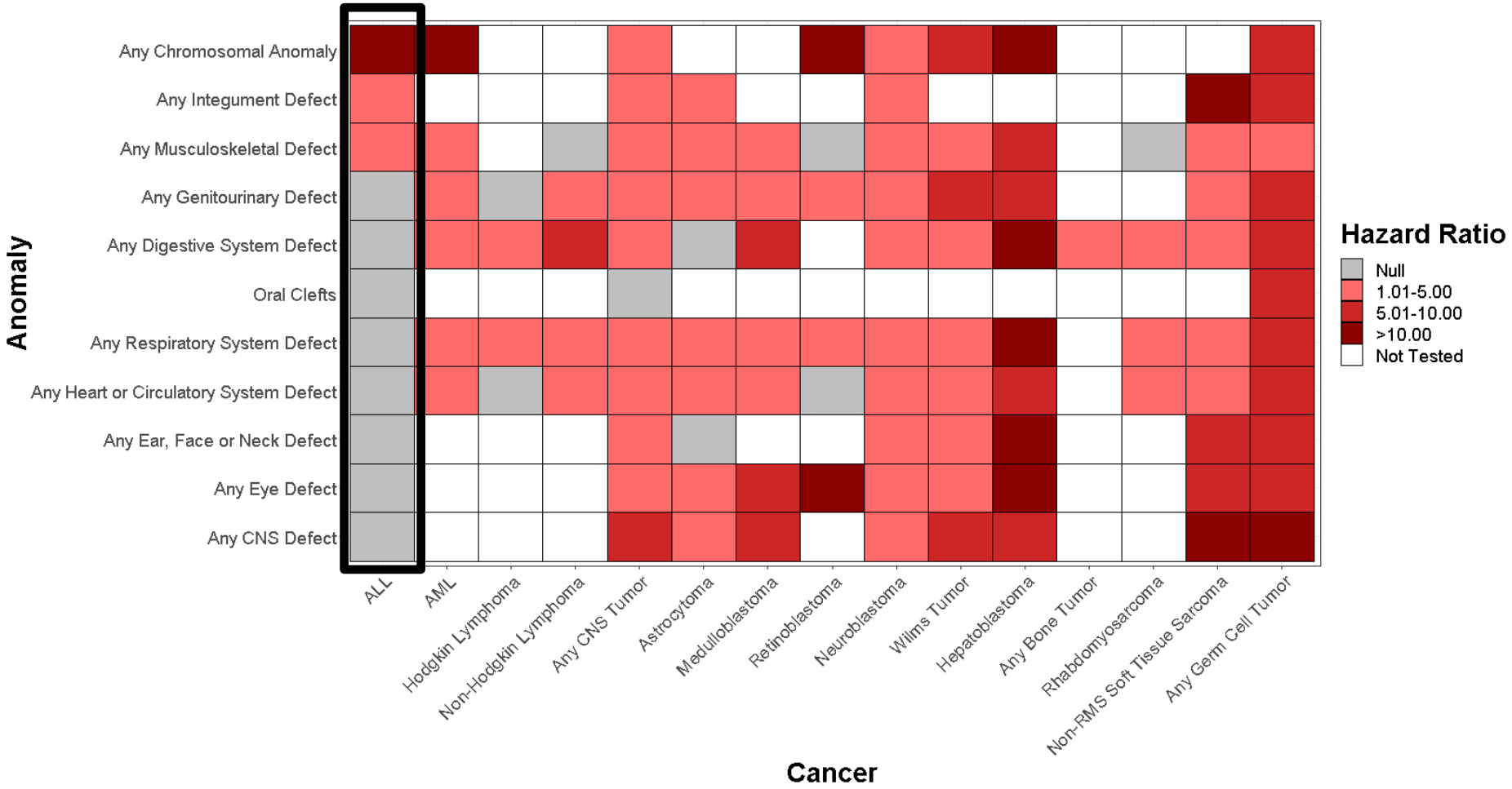
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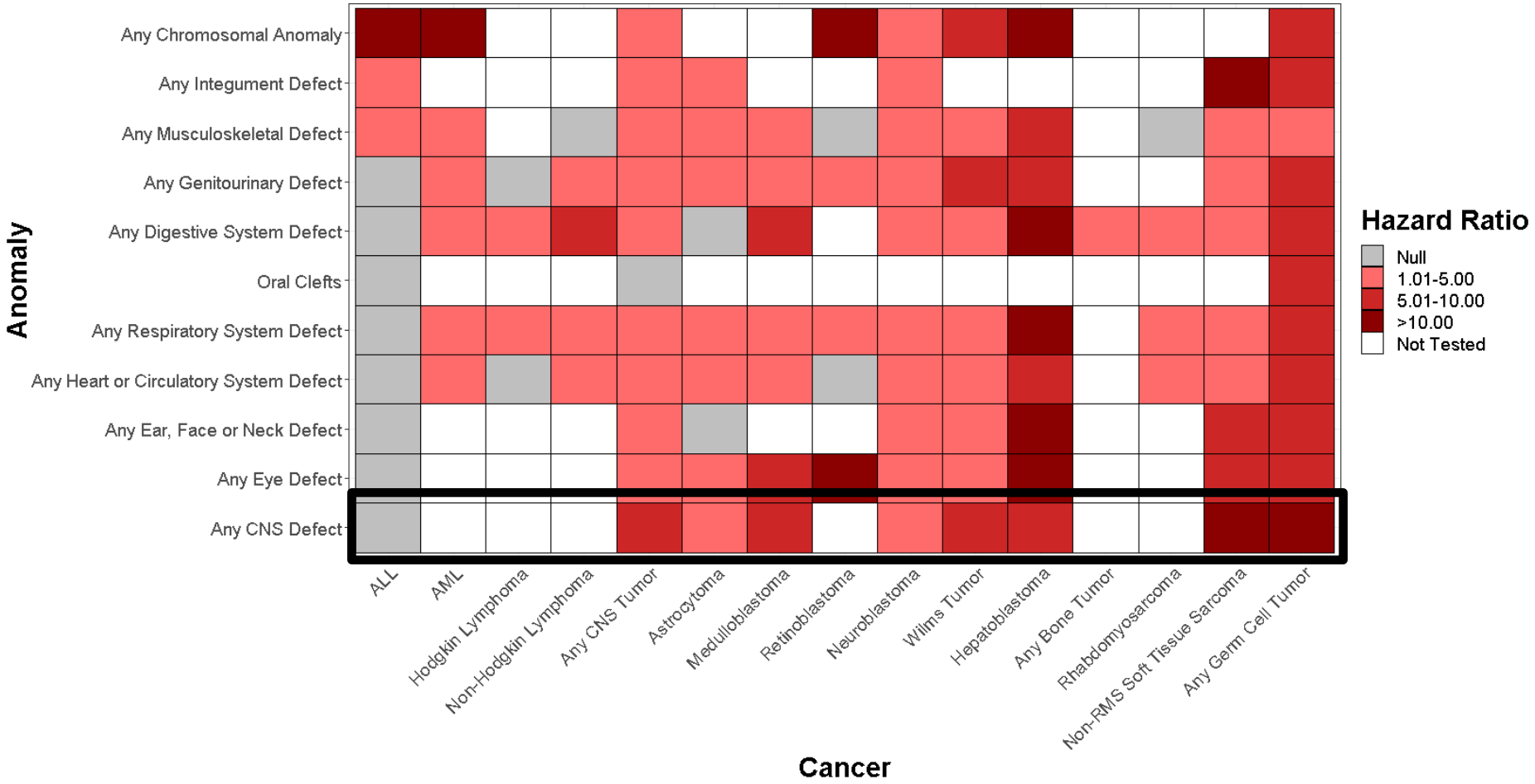
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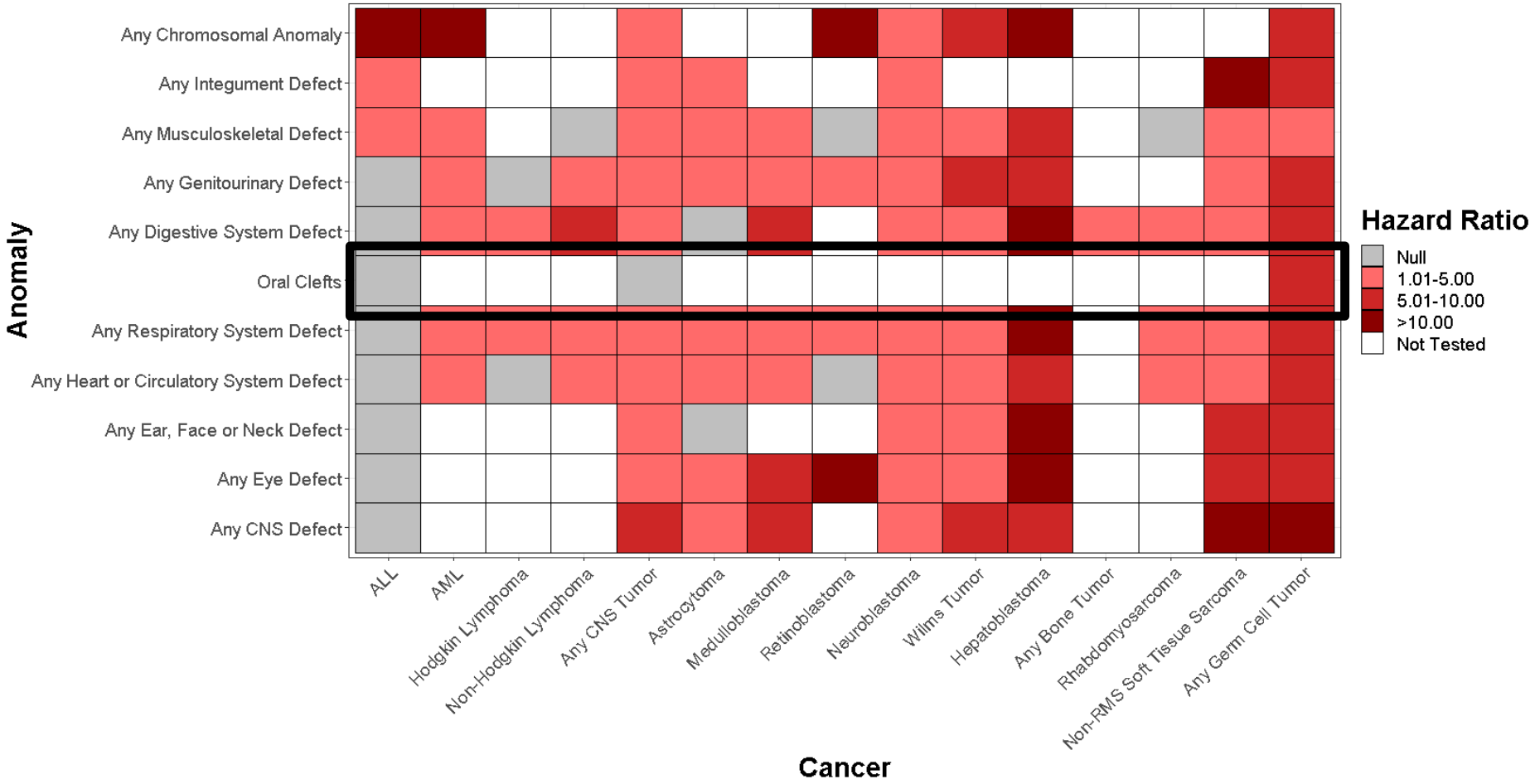
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Specific “non -syndromic” birth defect -cancer associations

- Tested 72 birth defect-cancer associations (≥5 co-occurring cases)

- 40 birth defect-cancer associations were significant after correcting for multiple comparisons

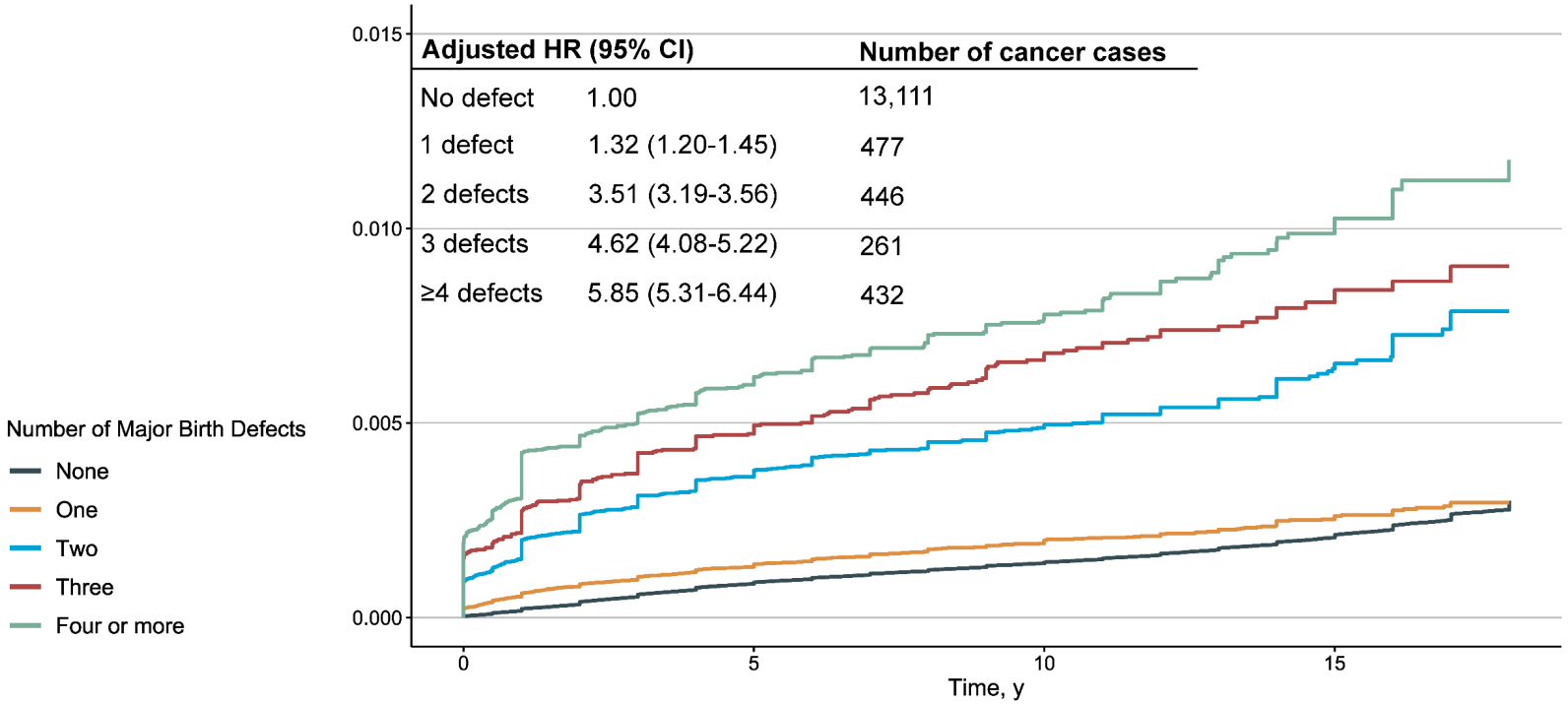
Non-syndromic birth defects and childhood cancer

Birth Defect	Cancer	HR (95% CI)[1]
Ventricular septal defect	Hepatoblastoma	10.6 (5.8-19.2)
Pulmonary valve atresia	Hepatoblastoma	22.6 (9.1-55.7)
Pulmonary valve atresia	Neuroblastoma	7.6 (3.8-15.3)
Left ventricular outflow tract defects	Neuroblastoma	7.8 (3.5-17.3)
Biliary atresia	Non-Hodgkin lymphoma	164.2 (77.8-346.8)
Craniosynostosis	Hepatoblastoma	9.7 (4.3-22.2)
Choanal atresia	**Acute leukemia**	**9.2 (3.8-22.1)**

1. Adjusted for maternal age, child's sex and state of birth. Models including hepatoblastoma are adjusted for birthweight. Models including ventricular septal defect are adjusted for birthweight and gestational age.

JAMA Oncol. 2019 Jun 20;5(8):1150-8

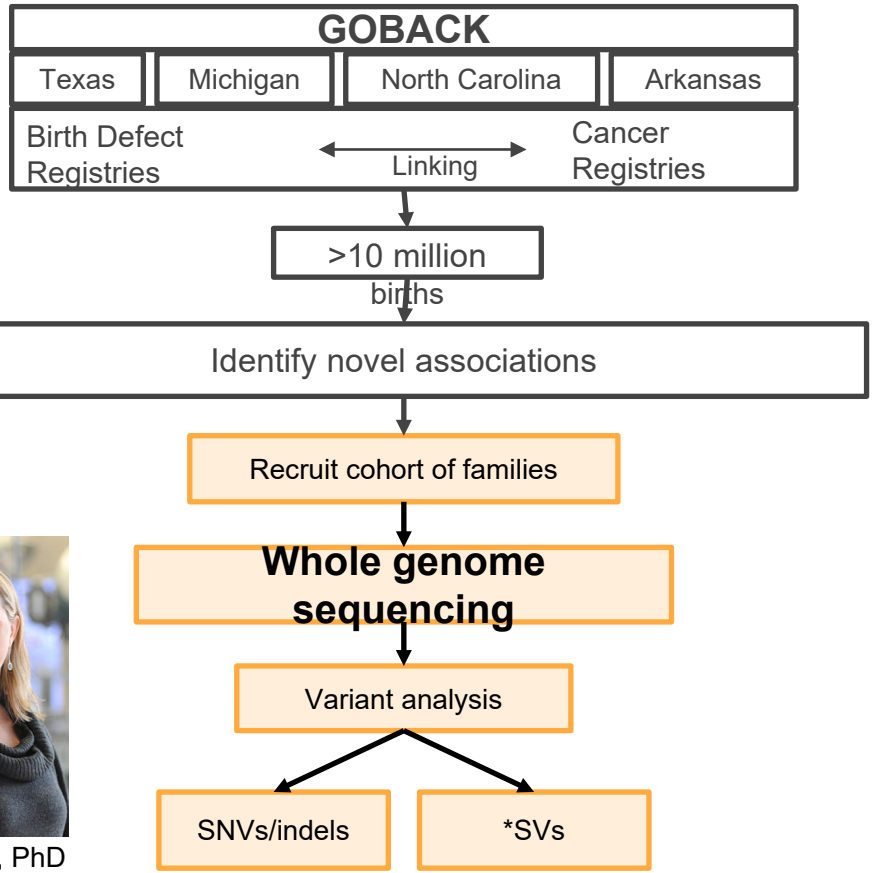
Cancer risk increased for children with multiple non -syndromic birth defects



JAMA Oncol. 2019 Jun 20;5(8):1150-8

GOBACK family cohort

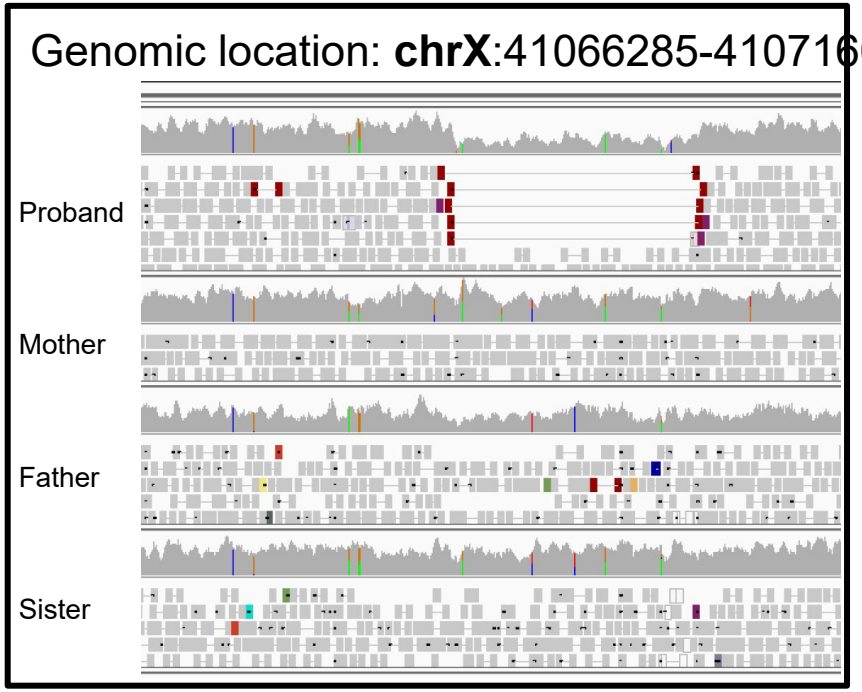
GOBACK
TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids

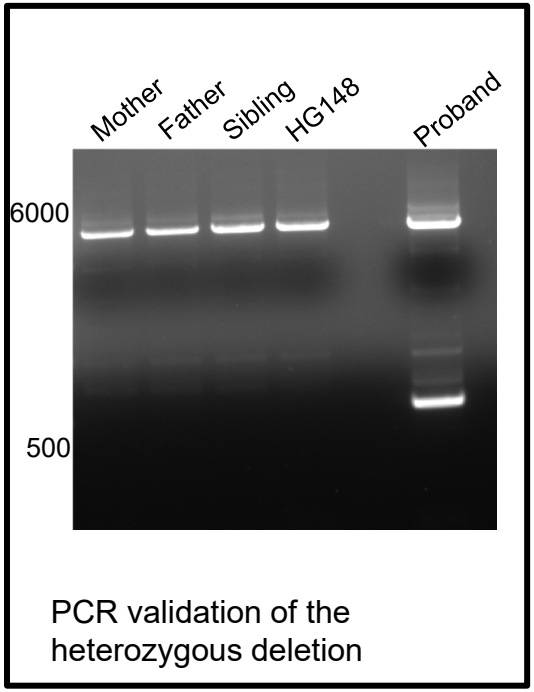


Sharon Plon, MD, PhD

Aniko Sabo, PhD

De novo ~5kb one exon deletion in *USP9X*





Saumya Sisoudiya

Phenotype of the proband

Female

Birth defects

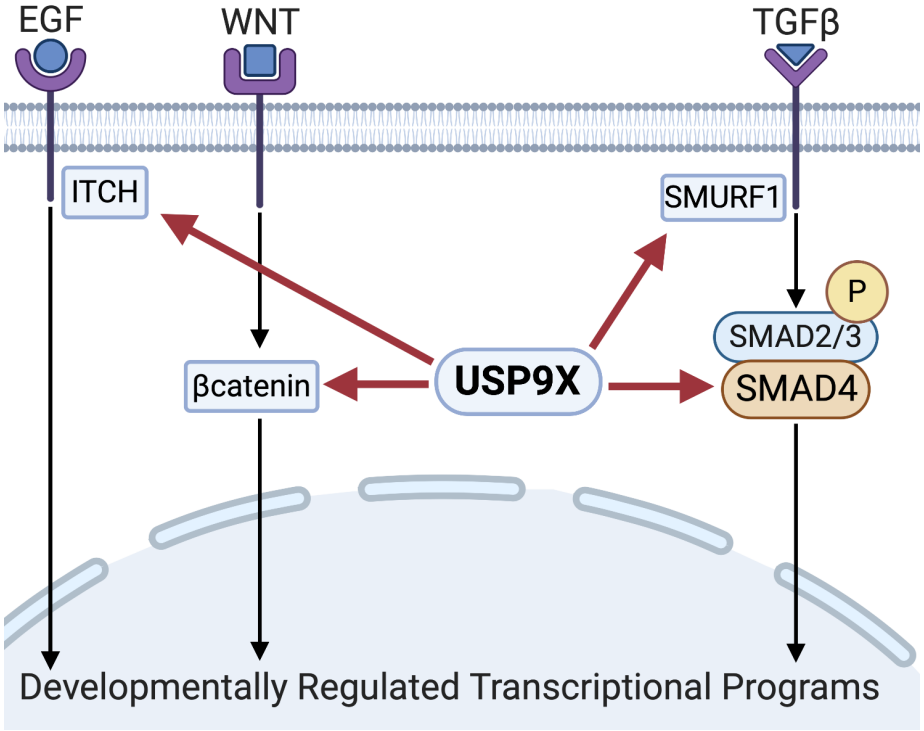
- Coloboma
- Heart defects
- **Choanal atresia**
- Ear anomalies
- Genitourinary anomalies

Indicative of CHARGE syndrome but did not have a *CHD7* pathogenic variant

Cancer: **Precursor cell lymphoblastic leukemia**

Choanal atresia-acute leukemia HR=9.2, 95% CI: 3.8-22.1

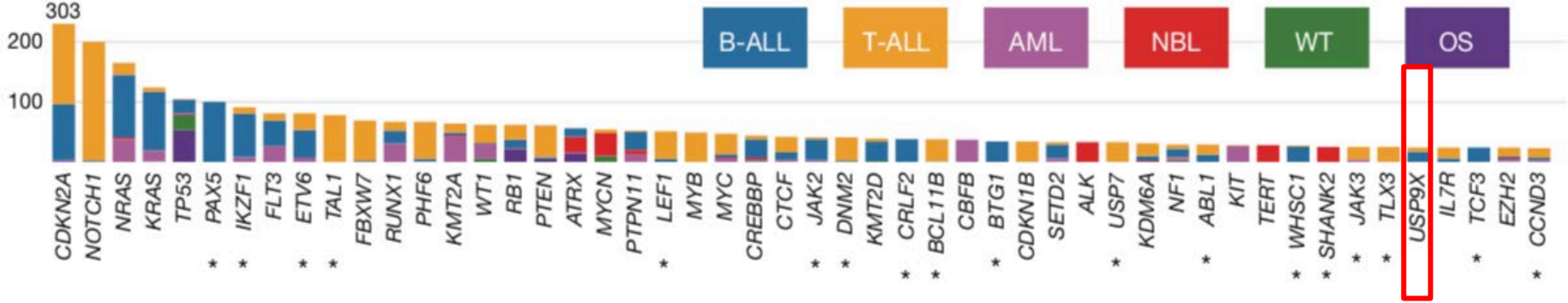
USP9X involved in several developmental and cancer pathways



Adapted from Murtaza et. al., *Cell and Mol Life Sci.*, 2015

Created with BioRender.com

USP9X somatically mutated in childhood cancers



Ma et al, Nature, 2018

Hypothesis: *USP9X* is a novel ALL susceptibility gene associated with a CHARGE-like syndrome

Next steps: Kids First GOBACK X01

CHILDREN'S ONCOLOGY GROUP

Leverage Children's Oncology Group Project:EveryChild (PEC)

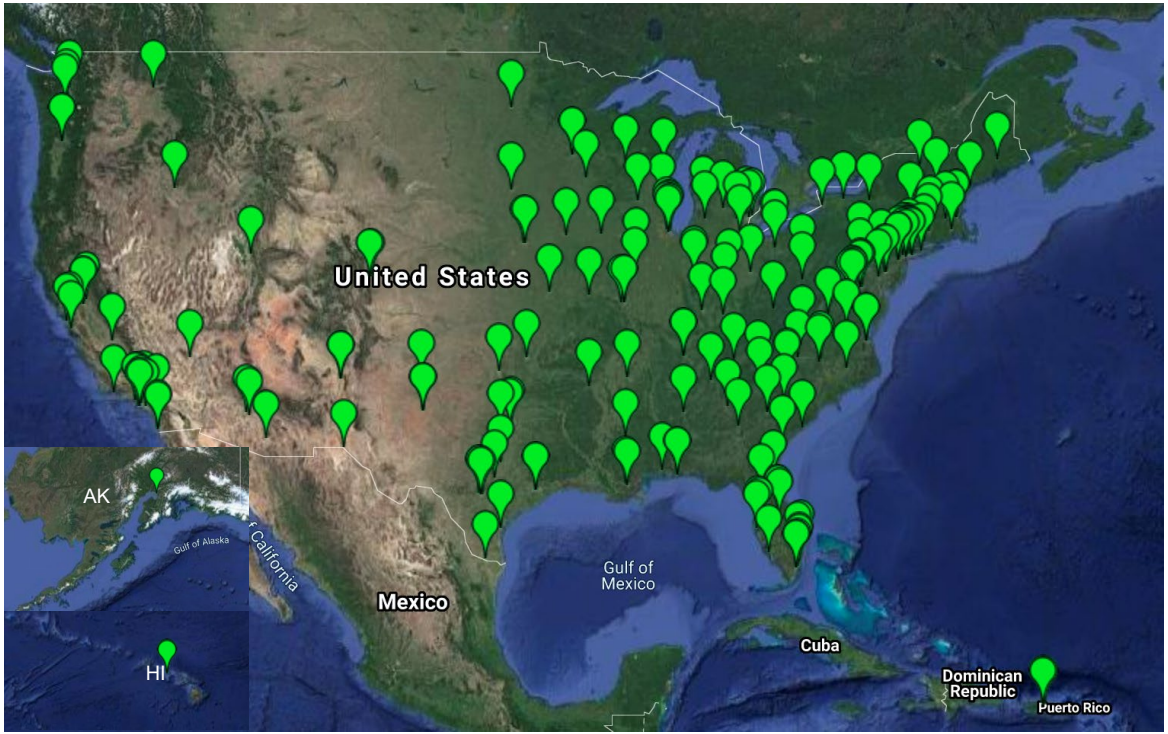
1. Determine the frequency of known cancer predisposition variants among children with congenital anomalies and cancer

2. Identify variants that underlie novel anomaly-cancer predisposition syndromes and describe the landscape of somatic alterations in these children

Gabriella Miller Kids First ATRIC RESEARCH PROGRAM

Sharon Plon
Logan Spector

Children's Oncology Group (COG)



~ 200 research sites throughout United States

~ 90% of children diagnosed with cancer in the US cared for at COG member sites

As of 2/2021

APEC14B1, Project EveryChild
Future Contact: optional information

PROJECT:EVERYCHILD

Patient Contact Information Child/Patient Initials _____ COG ID_____

Patient's Address: _____
Street Address

Patient's Address: _____
City (State/Province) (Zip /Postal Code)

Phone Number: _____ Country: _____ Email _____

*Driver's license number:*_____ *Driver's license issued state:* _____ (If applicable)

Parent/Guardian Future Contact Information

Parent/ Guardian: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____

First Parent or Guardian date of birth Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify_____

Parent/Guardian Future Contact Information

Parent/ Guardian: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____

Second Parent or Guardian date of birth Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify

Other Key Contact Information

Key Contact: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____

Key contact date of birth, if known Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify

APEC14B1, Project EveryChild Registry

PROJECT:EVERYCHILD

1. Where was the patient born?

City *State/Prov.* *Zip/Postal Code* *Country*

2. Was this patient a single or multiple birth?
☐ **Single** ☐ **Twins** ☐ **Triplets or more**
2a. If twin, specify: Identical Fraternal Unknown

2b. If twin, specify sex:
☐ Both female ☐ Both male ☐ Male/female

	No	Yes	Not sure
3. Was patient conceived through use of in vitro fertilization?	☐	☐	☐
4. Was cord blood banked at birth?	☐	☐	☐
5. Has anyone in the patient's immediate family (biological mother, father, brothers, sisters) ever had cancer? If yes, please record information below.	☐	☐	☐

My child's...	*What types of cancer?*
☐ Mother →	
☐ Father →	
☐ Full brother →	
☐ Full sister →	
☐ Son →	
☐ Daughter →	

6. Please indicate the name and relationship of at least one parent/guardian.

Parent or guardian: First Name *Last name*

Circle relationship: **Mother** **Father** **Grandparent** **Sibling**
Guardian ***Other relationship, specify:*** _____

7. Does the patient have any structural birth defects known at this time?

	No	Yes	Not sure
Cleft lip	☐	☐	☐
Cleft palate	☐	☐	☐
Clubfoot	☐	☐	☐
Gastroschisis	☐	☐	☐
Heart defect	☐	☐	☐
Other specify: _____	☐	☐	☐

8. Does the patient have any known genetic disorder?

	No	Yes	Not sure
Down Syndrome	☐	☐	☐
Li Fraumeni Syndrome	☐	☐	☐
Neurofibromatosis Type I	☐	☐	☐
Other specify: _____	☐	☐	☐

9. Does the patient have any known autoimmune diseases?

	No	Yes	Not sure
Juvenile Idiopathic Arthritis	☐	☐	☐
Celiac disease	☐	☐	☐
Diabetes mellitus (Type I)	☐	☐	☐
Inflammatory bowel diseases (Crohn's or Ulcerative colitis)	☐	☐	☐
Other specify: _____	☐	☐	☐

10. Which these describe the patient? Check all that apply.

[ ] - White
[ ] - African American
[ ] - American Indian, Aleutian, Eskimo
[ ] - Asian specify: _____
[ ] - Other specify: _____
[ ] - Unknown
[ ] - Non-Spanish, non-Hispanic
[ ] - Mexican (incl Chicano)
[ ] - Puerto Rican
[ ] - Cuban
[ ] - South or Central American (except Brazil)
[ ] - Other Spanish/Hispanic origin includes European

Please return to hospital or clinic staff. *Phone:* _____*FAX:* _____ ***Thank you for your information!***

Table 1. Number of non-syndromic congenital anomalies by tumor type in PEC, as of December 2020

Anomaly	Hematologic Malignancies	CNS Tumors	Non-CNS Solid Tumors	TOTAL
Spina Bifida	4	1	4	9
Central Nervous System	11	11	7	29
Eye	3	3	6	12
Ear, Face, and Neck	9	2	4	15
Heart	88	18	53	159
Circulatory	4	1	2	7
Respiratory	3	2	1	6
Clefts	14	4	4	22
Gastrointestinal	16	5	15	36
Genitourinary	28	6	27	61
Musculoskeletal	60	18	54	132
Integument	1	2	2	5
Other/unspecified	2	0	5	7
TOTAL	243	73	184	500

Kids First GOBACK Sequencing

- 700 blood and 500 tumor DNA samples for whole genome sequencing at 30X coverage
- 500 tumor DNA samples for whole exome sequencing at 100X coverage
- 120 tumor RNA samples for transcriptome sequencing

APEC14B1, Project EveryChild
Future Contact: optional information

PROJECT:EVERYCHILD

Patient Contact Information Child/Patient Initials _____ COG ID_____

Patient's Address: _____
Street Address

Patient's Address: _____
City (State/Province) (Zip /Postal Code)

Phone Number: _____ Country: _____ Email _____

*Driver's license number:*_____ *Driver's license issued state:* _____ (If applicable)

Parent/Guardian Future Contact Information

Parent/ Guardian: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____

First Parent or Guardian date of birth Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify_____

Parent/Guardian Future Contact Information

Parent/ Guardian: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____

Second Parent or Guardian date of birth Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify

Other Key Contact Information

Key Contact: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____

Key contact date of birth, if known Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify

APEC14B1, Project EveryChild Registry

PROJECT:EVERYCHILD

1. Where was the patient born?

City *State/Prov.* *Zip/Postal Code* *Country*

2. Was this patient a single or multiple birth?
☐ **Single** ☐ **Twins** ☐ **Triplets or more**
2a. If twin, specify: Identical Fraternal Unknown

2b. If twin, specify sex:
☐ Both female ☐ Both male ☐ Male/female

	No	Yes	Not sure
3. Was patient conceived through use of in vitro fertilization?	☐	☐	☐
4. Was cord blood banked at birth?	☐	☐	☐
5. Has anyone in the patient's immediate family (biological mother, father, brothers, sisters) ever had cancer? If yes, please record information below.	☐	☐	☐

My child's...	*What types of cancer?*
☐ Mother →	
☐ Father →	
☐ Full brother →	
☐ Full sister →	
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Cleft palate	☐	☐	☐
Clubfoot	☐	☐	☐
Gastroschisis	☐	☐	☐
Heart defect	☐	☐	☐
Other specify: _____	☐	☐	☐

8. Does the patient have any known genetic disorder?

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Li Fraumeni Syndrome	☐	☐	☐
Neurofibromatosis Type I	☐	☐	☐
Other specify: _____	☐	☐	☐

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Celiac disease	☐	☐	☐
Diabetes mellitus (Type I)	☐	☐	☐
Inflammatory bowel diseases (Crohn's or Ulcerative colitis)	☐	☐	☐
Other specify: _____	☐	☐	☐

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[ ] - Cuban
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Please return to hospital or clinic staff. *Phone:* _____*FAX:* _____ ***Thank you for your information!***

Kids First GOBACK R03

1. Collect extensive phenotypic and clinical data from children with congenital anomalies and cancer enrolled in Project:EveryChild

2. Integrate phenotypic and clinical data from Project:EveryChild into the Gabriella Miller Kids First Pediatric Data Resource Center

Allison Heath
Adam Resnick

GOBACK conclusions

- Population-based registries can be leveraged to inform genomic analyses
- Birth defects could account for ~10% of childhood cancers
- Non-syndromic birth defects are associated with an increased risk for childhood cancer, especially embryonal tumors and germ cell tumors
- Reasons for these associations are complex and multifactorial: **in some children, inherited and *de novo* genetic variants likely explain both phenotypes**

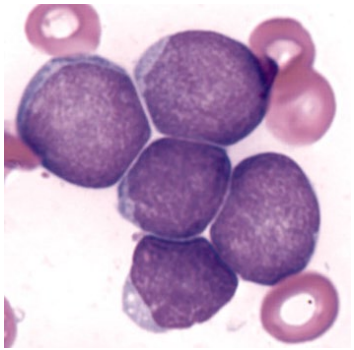
GOBACK TO THE BASES

Overlap Between
es and Cancer in Kids

Down syndrome -associated leukemia

Down syndrome (DS) and leukemia

- First reported 1930
- First systematic study in 1957
- ~20-fold increased risk
- Cumulative risk of 2% by age 5
- Comprises ~2% of childhood acute lymphoblastic leukemia (ALL) and 10% of childhood acute myeloid leukemia (AML)



Hasle et al, Lancet 200

Clinical features of DS -ALL

- Similar age range, except rare in infants
- Distinctive immunophenotype - T-ALL and Burkitt very rare
- Distinctive spectrum of genetic alterations
  - Typical ALL alterations (hyperdiploidy, *ETV6-RUNX1*) less common
  - *CRLF2*-R and *JAK* alterations more common
- Poorer outcomes
  - Increased risk of relapse
  - Increased treatment-related mortality, primarily infections

Li et al, Leukemia 2016
Buitenkamp et al, Blood 2014

Why does ALL arise more often in children with DS?

- Are there germline genetic variants associated with the ALL susceptibility in children with DS?

- How do germline and somatic variants interact within the context of trisomy 21?

Genome-wide Association Studies (GWASs) of non-DS ALL

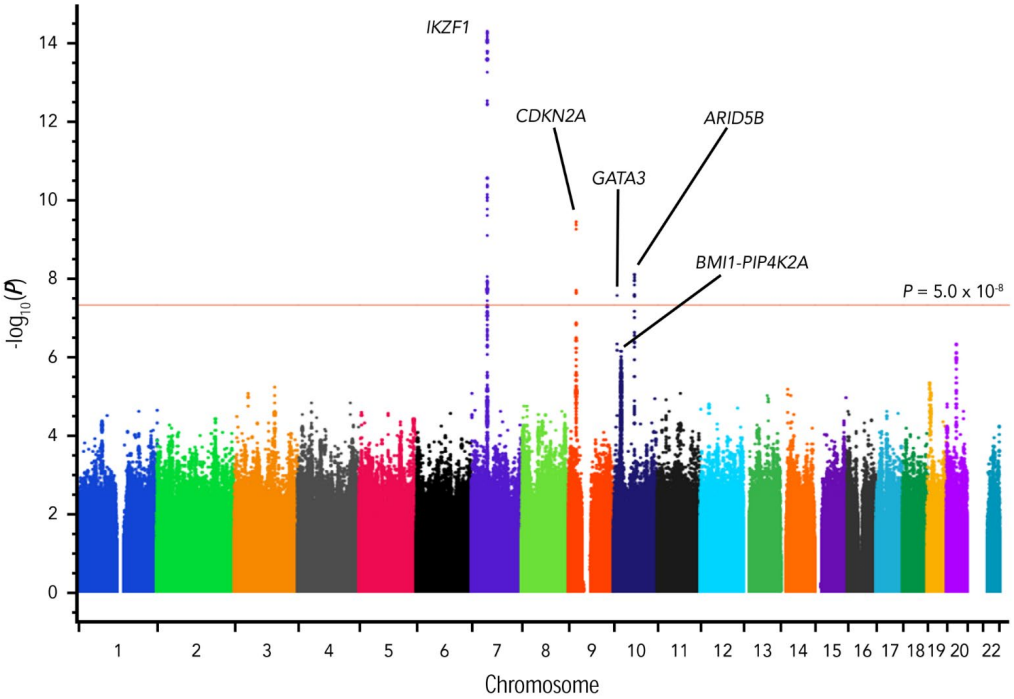
Gene	Chr	SNP	OR (95% CI)	P-value	Reference
ARID5B	10	rs10821936	1.86 (1.71-2.03)	5.9×10^{-46}	Xu et al. 2013
ARID5B	10	rs7089424	1.65 (1.54-1.76)	6.7×10^{-19}	Papaemmanuil et al. 2009
IKZF1	7	rs11978267	1.59 (1.45-1.74)	5.3×10^{-24}	Xu et al. 2013
IKZF1	7	rs6944602	1.64 (1.37-2.07)	3.4×10^{-15}	Papaemmanuil et al. 2009
CDKN2A	9	rs3731249	2.23 (1.90-2.61)	9.0×10^{-23}	Xu et al. 2015
CDKN2A	9	rs17756311	1.36 (1.18-1.56)	1.4×10^{-5}	Xu et al. 2013
CEBPE	14	rs4982731	1.36 (1.24-1.48)	9.0×10^{-12}	Xu et al. 2013
PIP4K2A	10	rs7088318	1.40 (1.28-1.53)	1.1×10^{-11}	Xu et al. 2013
GATA3	10	rs3824662	3.85 (2.71-5.47)	2.2×10^{-14}	Perez-Andreu et al. 2013

GWAS of ALL susceptibility in children with DS

- Objectives
  - Identify inherited genetic variants associated with ALL susceptibility in DS
  - Explore association between inherited variation and common somatic alterations
  - Compare frequency of established risk alleles in ALL cases with vs without DS
- Meta-analysis of 4 cohorts
- Cases – children with DS ALL (n=542)
- Controls – children with DS, no ALL (n=1,192)

Brown et al, Blood 2019

GWAS findings: ALL susceptibility in children with DS



SNP	Chr	Pos	Gene	Meta-analysis (542 DS-ALL cases, 1192 DS controls)	
				OR (95% CI)	P
rs58923657	7	50472842	*IKZF1*	2.02 (1.70-2.41)	5.32e-15
rs3731249*	9	21970916	*CDKN2A*	3.63 (2.42-5.43)	3.91e-10
rs7090445	10	63721176	*ARID5B*	1.60 (1.36-1.88)	8.44e-9
rs3781093	10	8101927	*GATA3*	1.73 (1.43-2.10)	2.89e-8

Brown et al, Blood 2019

Table 3. Results from case-case analysis of association between ALL risk alleles and DS status

SNP	Pos	Gene	DS-ALL COG molecular subgroup adjusted comparison‡ (255 DS-ALL, 2387 non-DS ALL)	
			OR (95% CI)	*P*
rs11978267	Chr7:50466304	*IKZF1*	0.97 (0.77-1.23)	.820
rs3731249	Chr9:21970916	*CDKN2A*	1.72 (1.10-2.69)	.017
rs3824662	Chr10:8104208	*GATA3*	0.81 (0.63-1.06)	.121
rs12769953	Chr10:22407656	*BMI1*	1.12 (0.83-1.50)	.461
rs10741006	Chr10:22856019	*PIP4K2A*	0.96 (0.75-1.23)	.759
rs7089424	Chr10:63752159	*ARID5B*	0.80 (0.64-1.01)	.056
rs2239633	Chr14:23589057	*CEBPE*	1.17 (0.92-1.47)	.199

‡Analysis adjusted for top 5 principal components and molecular subgroups (CRLF2 high, high hyperdiploidy, *ETV6-RUNX1*, and B other).

Brown et al, Blood 2019

Table 4. Results from subgroup-specific case-case analysis of association between ALL risk alleles and DS status

SNP	Position	Gene	CRLF2-high (151 DS-ALL, 55 non-DS ALL)		High hyperdiploid (19 DS-ALL, 888 non-DS ALL)		*ETV6-RUNX1* (45 DS-ALL, 547 non-DS ALL)		B-other (40 DS-ALL, 859 non-DS ALL)	
			OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
rs11978267	Chr7:50466304	*IKZF1*	0.71 (0.48-1.05)	.08	1.26 (0.67-2.36)	.47	0.89 (0.55-1.45)	.65	1.37 (0.87-2.17)	.17
rs3731249	Chr9:21970916	*CDKN2A*	2.16 (0.96-4.89)	.06	1.62 (0.49-5.43)	.43	1.68 (0.64-4.39)	.29	1.49 (0.60-3.68)	.39
rs3824662	Chr10:8104208	*GATA3*	0.73 (0.50-1.06)	.10	1.02 (0.48-2.20)	.95	1.02 (0.59-1.78)	.94	0.74 (0.42-1.29)	.29
rs12769953	Chr10:22407656	*BMI1*	1.28 (0.78-2.11)	.33	1.52 (0.58-3.95)	.40	0.75 (0.45-1.22)	.24	1.45 (0.76-2.77)	.26
rs10741006	Chr10:22856019	*PIP4K2A*	0.85 (0.56-1.31)	.47	0.75 (0.38-1.48)	.41	0.78 (0.49-1.23)	.28	1.73 (1.00-2.97)	.04
rs7089424	Chr10:63752159	*ARID5B*	0.45 (0.30-0.67)	1.0e-4	1.38 (0.70-2.74)	.36	1.02 (0.65-1.61)	.93	1.06 (0.68-1.66)	.80
rs2239633	Chr14:23589057	*CEBPE*	1.35 (0.93-1.98)	.12	0.92 (0.47-1.80)	.81	1.19 (0.76-1.88)	.45	1.01 (0.62-1.63)	.99

*Analyses comparing DS-ALL and non-DS ALL cases enrolled on COG P9900 or AALL0232 trials. *P* values and ORs calculated using logistic regression tests assuming additive allelic effects, adjusting for the top 5 principal components.

Brown et al, Blood 2019

GWAS conclusions

- Established non-DS ALL susceptibility loci also contribute to ALL risk in children with DS
  - Genome-wide significance loci at *IKZF1*, *CDKN2A*, *ARID5B*, *GATA3*

- Rather than exhibiting unique susceptibility loci, trisomy 21 appears to modify penetrance of inherited ALL susceptibility
  - Greater magnitude of effect, particularly for *CDKN2A*

Next steps

Whole genome sequencing (WGS) for comprehensive analysis of heritable variation associated with ALL in children with DS

NIH National Institutes of Health
Turning Discovery Into Health

INCLUDE PROJECT

Gabriella Miller Kids First
PEDIATRIC RESEARCH PROGRAM

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

Collaboration: WGS in DS -ALL and AVSD

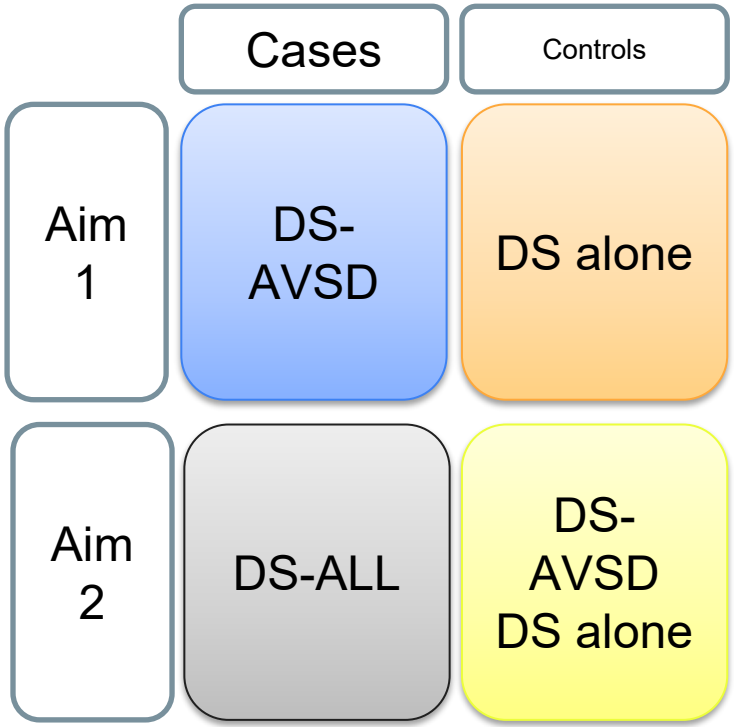
- Children with DS have 2,000-fold increased risk of atrioventricular septal defect (AVSD) and 10-fold increased risk of ALL
- Genetic factors underlying these associations unknown

- **Central hypothesis:** risk-associated genetic variants in the background of trisomy 21 lead to higher penetrance of AVSD and ALL
- **Secondary hypothesis:** rare variants explain a significant proportion of this increased risk

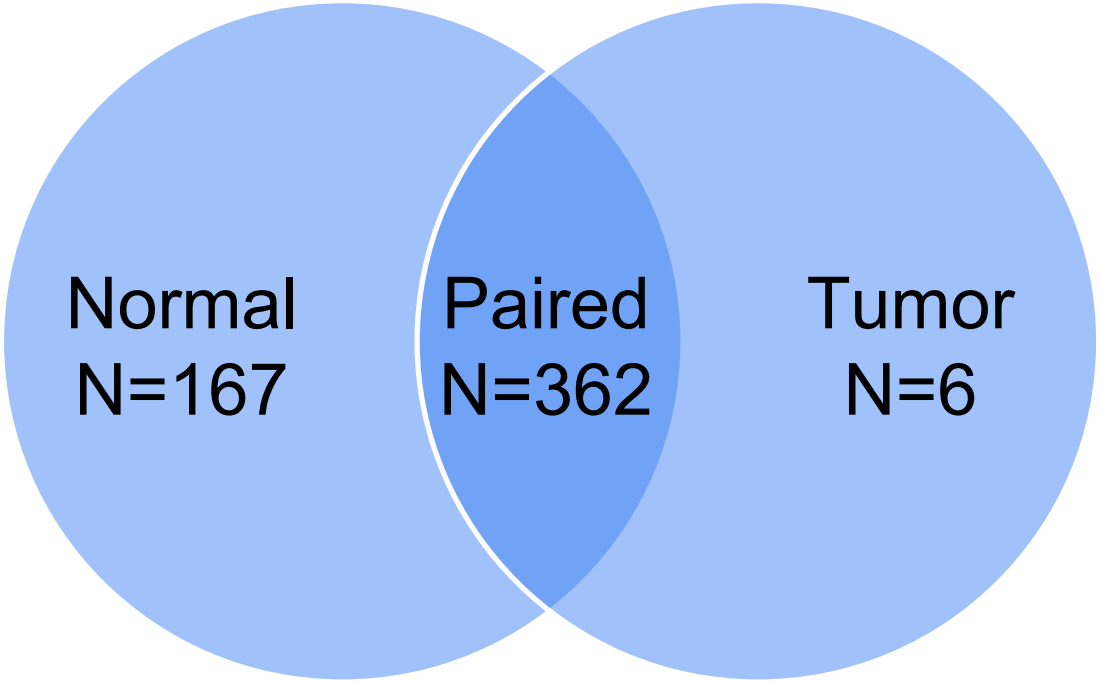
Karen Rabin
Jun Yang
Stephanie Sherman

Kids First DS -ALL X01

1. Identify genetic variants underlying AVSD in children with DS
2. Identify genetic variants underlying ALL in children with DS
    - Particular attention to rare, structural, and chromosome 21 variants
    - Evaluation of relationship between germline and somatic features (WGS of paired leukemia-germline samples)



DS-ALL sequencing: normal and tumor samples



Plans underway

- **Perform a comprehensive analysis of heritable variation associated with risk of ALL in children with DS**
  - Assess structural, rare, and chr21 variants
  - Evaluate relationship between the inherited genome and somatic features

- **Conduct deep phenotyping of children with DS-ALL to identify congenital risk factors for DS-ALL and their impact on leukemia clinical features and outcomes**
  - Determine co-occurring conditions among children in COG biology and/or registry protocols
  - Link to other data resources

DS-ALL conclusions

- Children with DS and ALL have a distinctive clinical presentation, which reflects underlying differences in somatic alterations and germline risk factors
- Known non-DS ALL susceptibility loci also contribute to ALL risk in children with DS, but with differing effect sizes
- Rare, structural, and chr21 variants may also explain a proportion of ALL risk

Overall conclusions

- Kids First provides a unique opportunity to explore the overlap between birth defects and cancer
- Some associations may be driven by uncharacterized syndromes – Kids First data can be leveraged to explore this possibility
- Insights into factors influencing cancer among children with birth defects may guide improved genetic counseling, surveillance, and treatment interventions

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

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Texas Children's Cancer Center

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- Marcia Fournier

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GOBACK
TO THE BASES

Genetic Overlap Between Anomalies and Cancer in Kids

Email: GOBACK_Study@bcm.edu | T 1-855-474-4520

Baylor College of Medicine

Texas Children's Cancer Center

Adam Resnick, PhD

Co Director

Center for Data Driven Discovery in Biomedicine
Children's Hospital of Philadelphia

Adam Resnick

@adamcresnick

David Higgins, PhD

Informatics Program Manager

Center for Data Driven Discovery in Biomedicine
Children's Hospital of Philadelphia

David Higgins

Kids First Variant Search Tool: Exploring Datasets to Jump Start Analyses

Gabriella Miller Kids First
PEDIATRIC RESEARCH PROGRAM

Kids First Variant Search Tool:
Exploring Datasets to Jump Start Analyses

Kids First Spring Public Webinar
May 13th, 2022

Follow **@kidsfirstdrc**

Visit **kidsfirstdrc.org**

Gabriella Miller Kids First Data Resource Center

20,267 Participants

8,462 Families

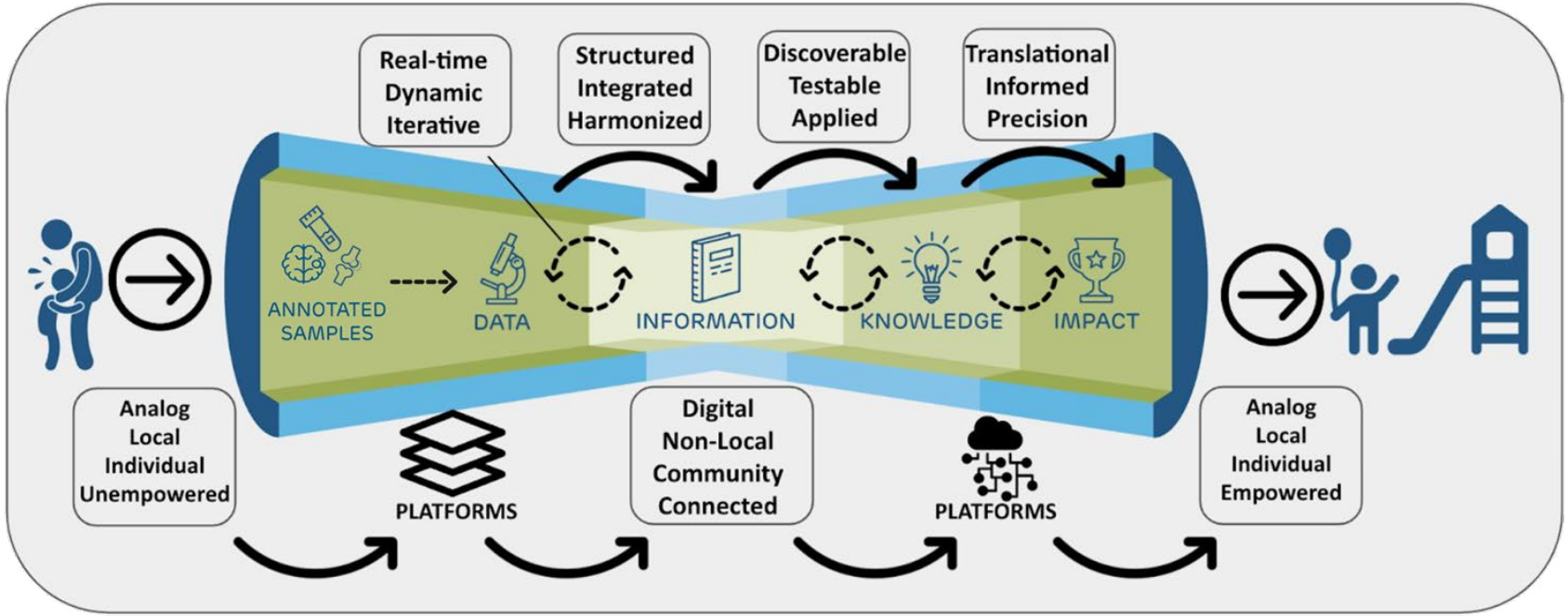
81,927 Files

1.09 PB of Data

24 Studies Released on the Portal

- Kids First: Orofacial Cleft: African and Asian Ancestry
- Kids First: Neuroblastoma
- Kids First: Myeloid Malignancies
- Kids First: Esophageal Atresia & Tracheoesophageal Fistulas
- Kids First: Disorders of Sex Development
- Kids First: Leukemia & Heart Defects in Down Syndrome
- Kids First: Novel Cancer Susceptibility in Families (from BASIC3)
- Kids First: Congenital Diaphragmatic Hernia
- Kids First: Enchondromatosis
- Kids First: Orofacial Cleft – European Ancestry
- Kids First: T Cell ALL
- Kids First: Microtia – HIspanic
- Kids First: Intersections of Cancer & SBD
- Kids First: Orofacial Cleft – Latin American
- Kids First: Familial Leukemia
- Kids First: Craniofacial Microsomia
- Kids First: Syndromic Cranial Dysinnervation
- Kids First: Kidney and Urinary Tract Defects
- Kids First: Adolescent Idiopathic Scoliosis
- Kids First: Hemangiomas (PHACE)
- Kids First: Ewing Sarcoma
- Kids First: Nonsyndromic Craniosynostosis
- Kids First: Congenital Heart Defects
- Kids First: Osteosarcoma

Gabriella Miller Kids First Data Resource Center



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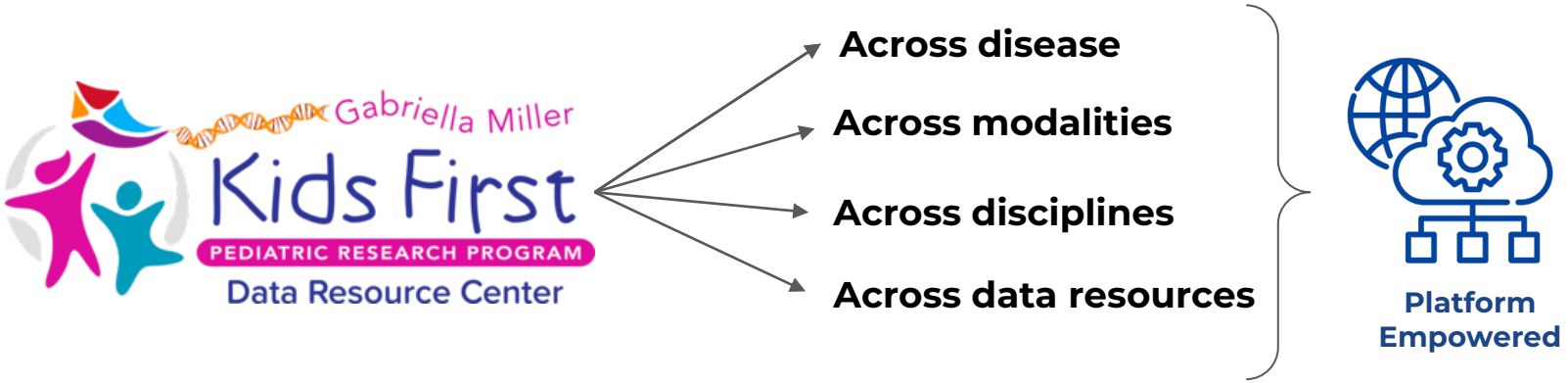

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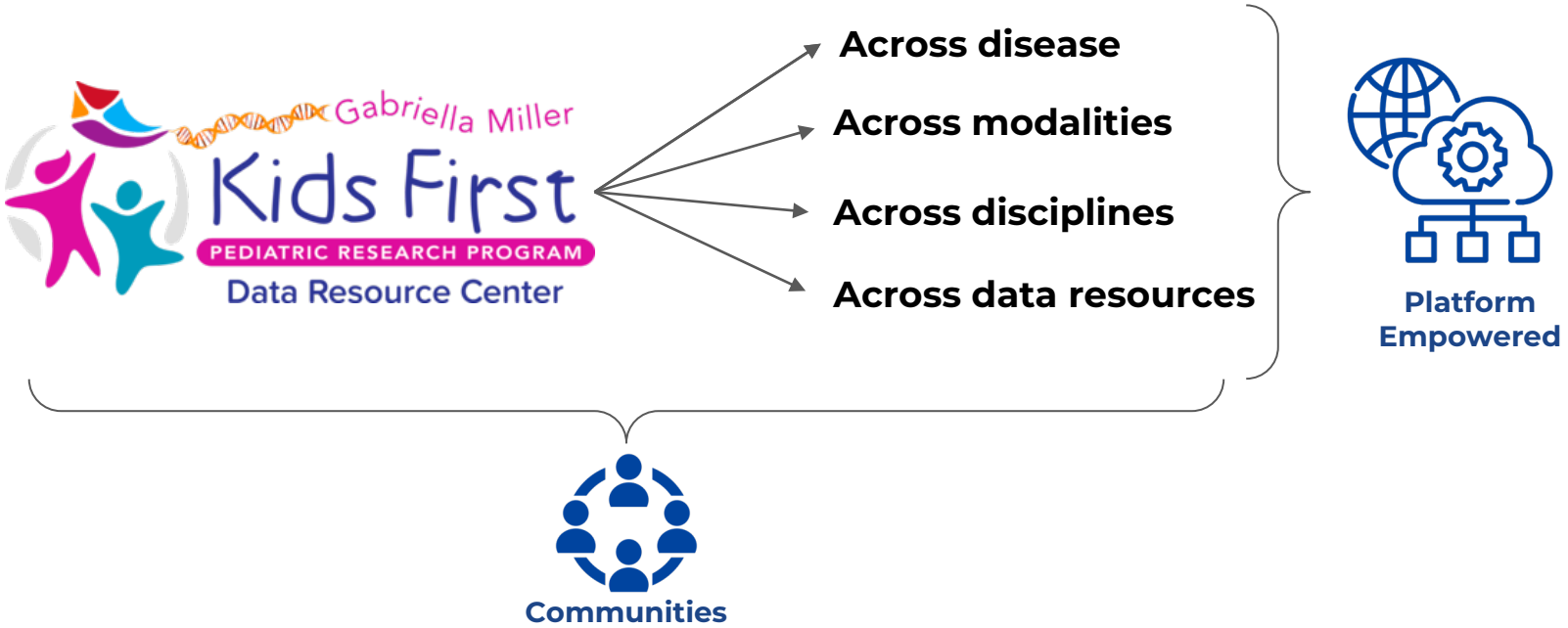
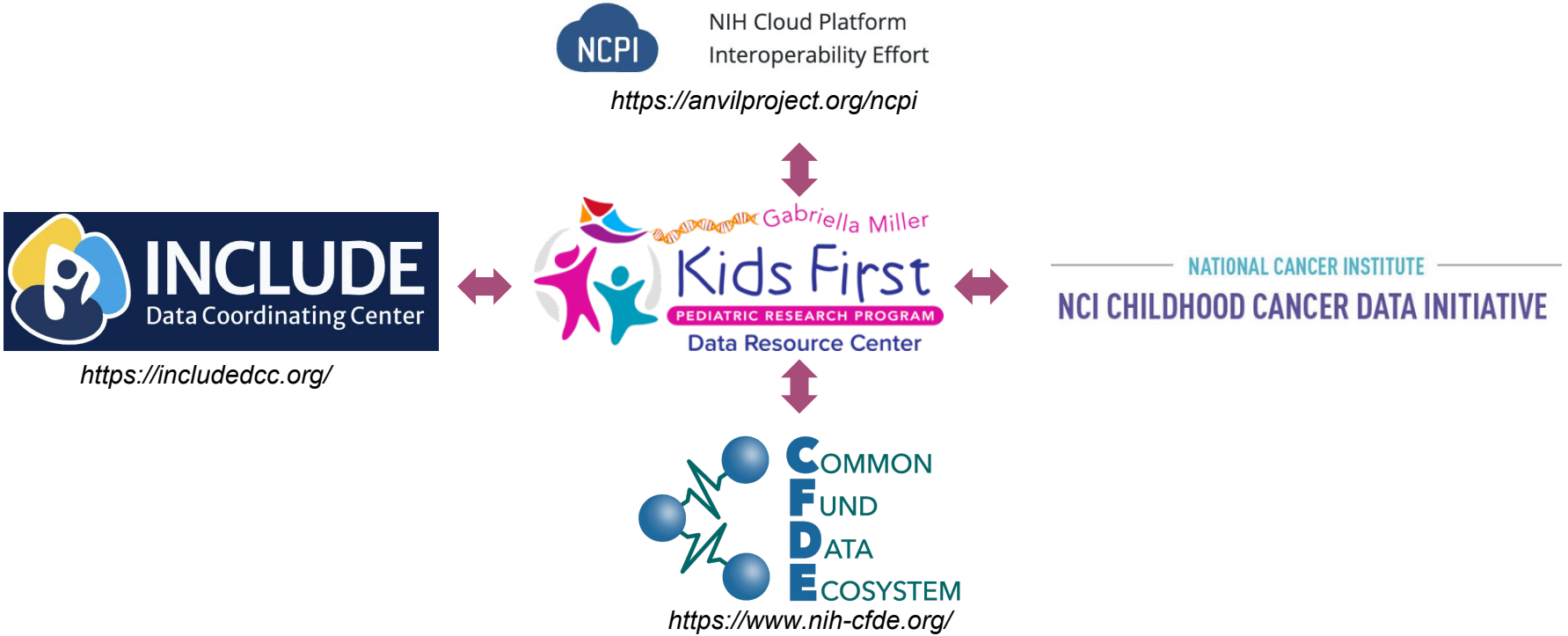


KFDRC: Connectivity on behalf of discovery



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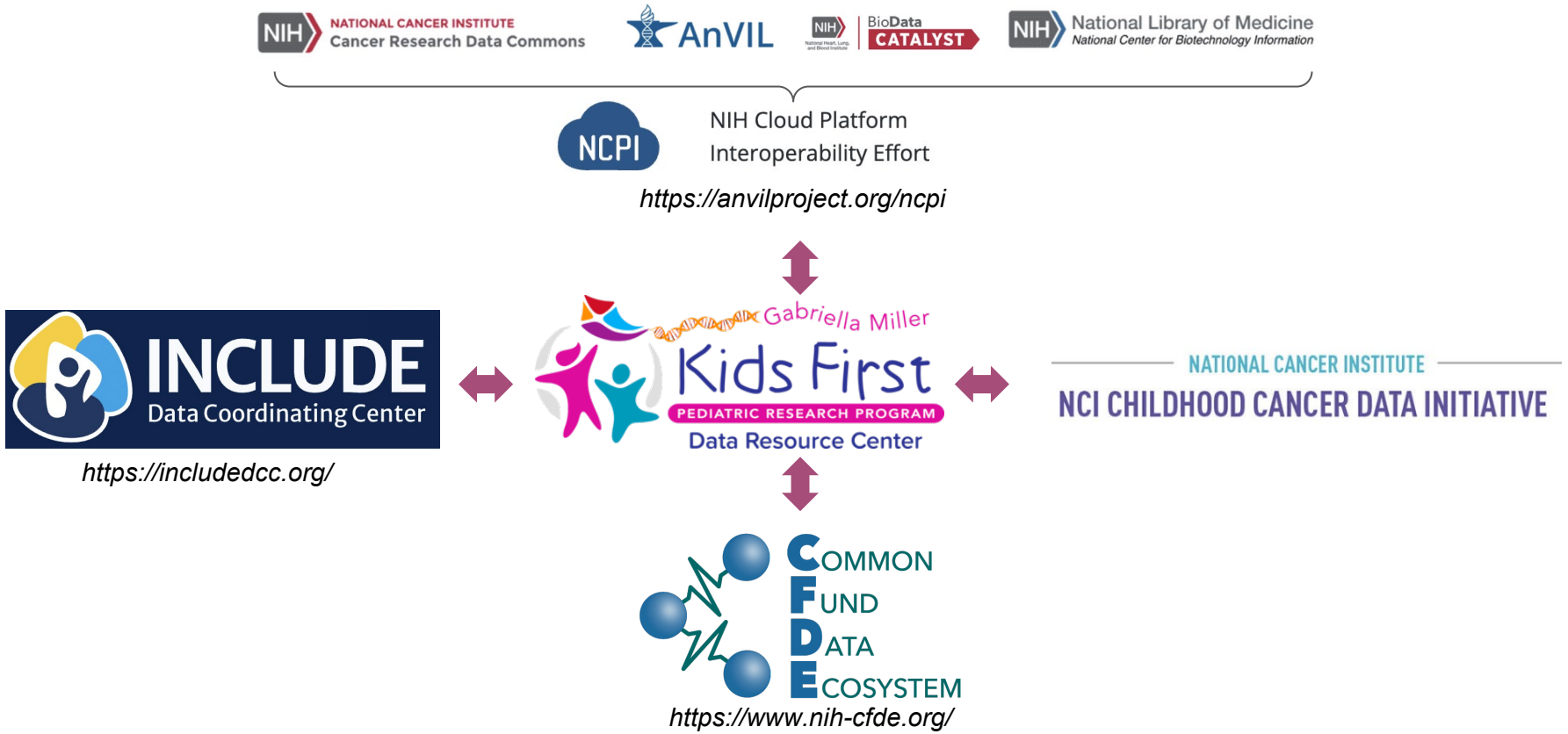

Variant Search Tool

Acknowledgements - Variant Search Tool

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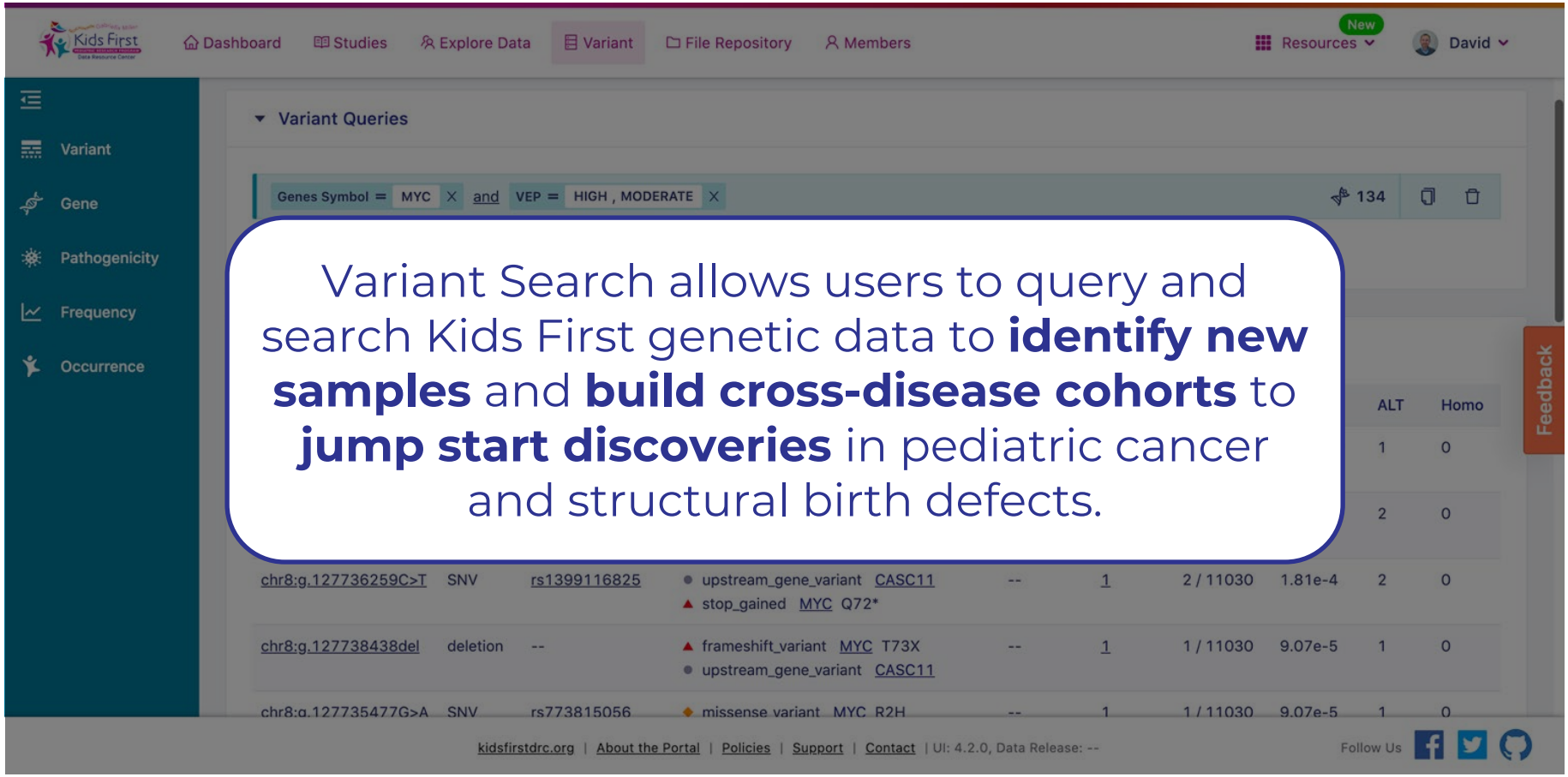
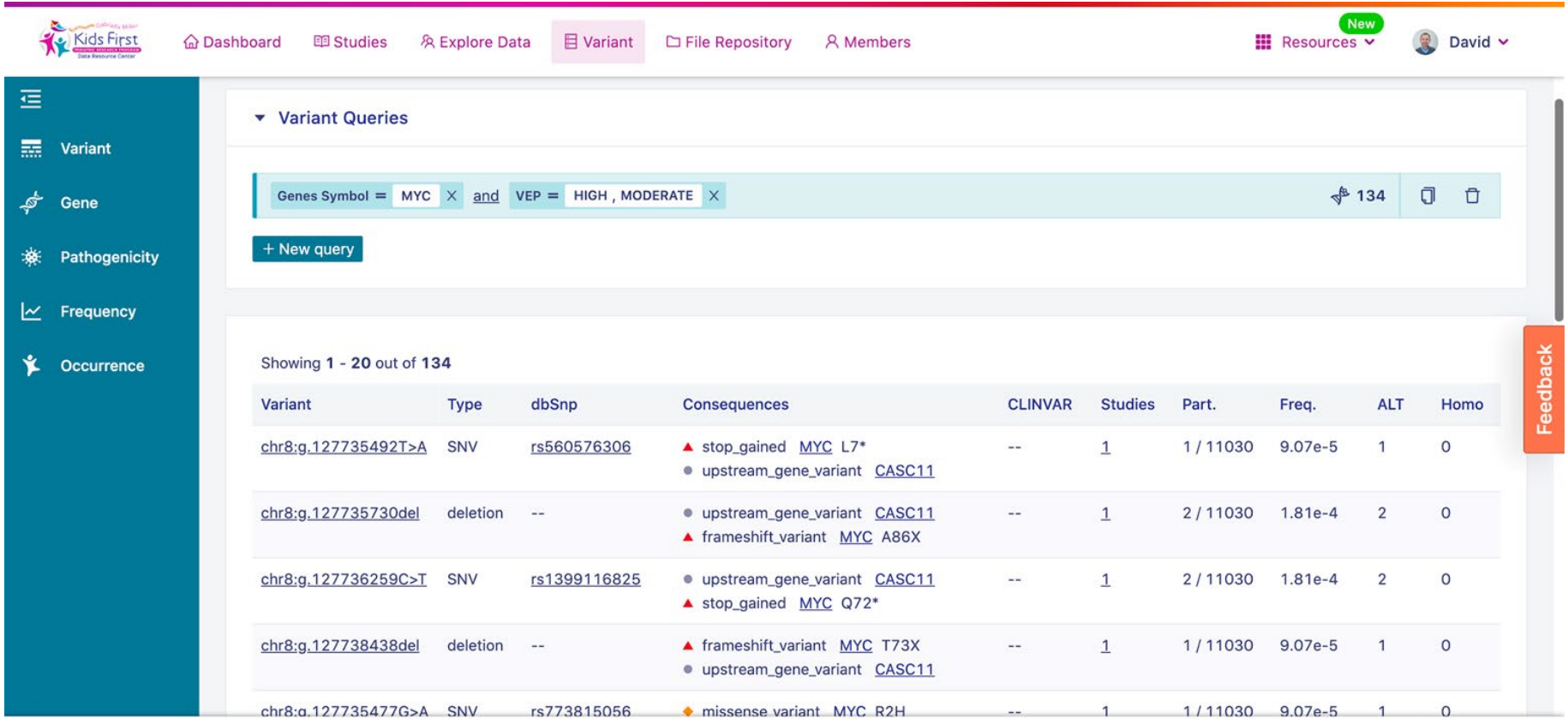
Evans Girard
Francis Iavoie
Lucas Lemmonier

Kids First Variant Search Tool

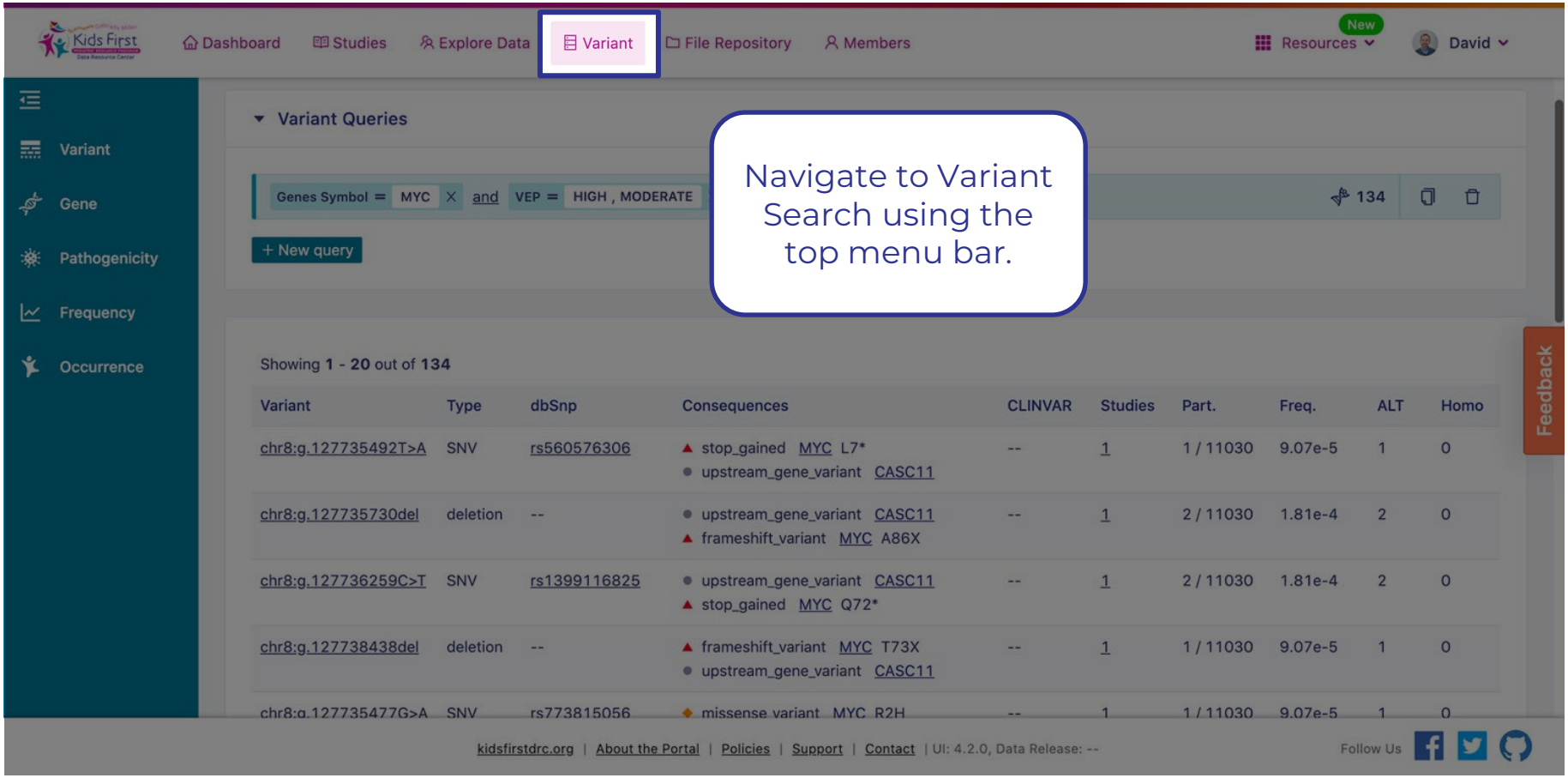


Variant Search allows users to query and search Kids First genetic data to **identify new samples** and **build cross-disease cohorts** to **jump start discoveries** in pediatric cancer and structural birth defects.

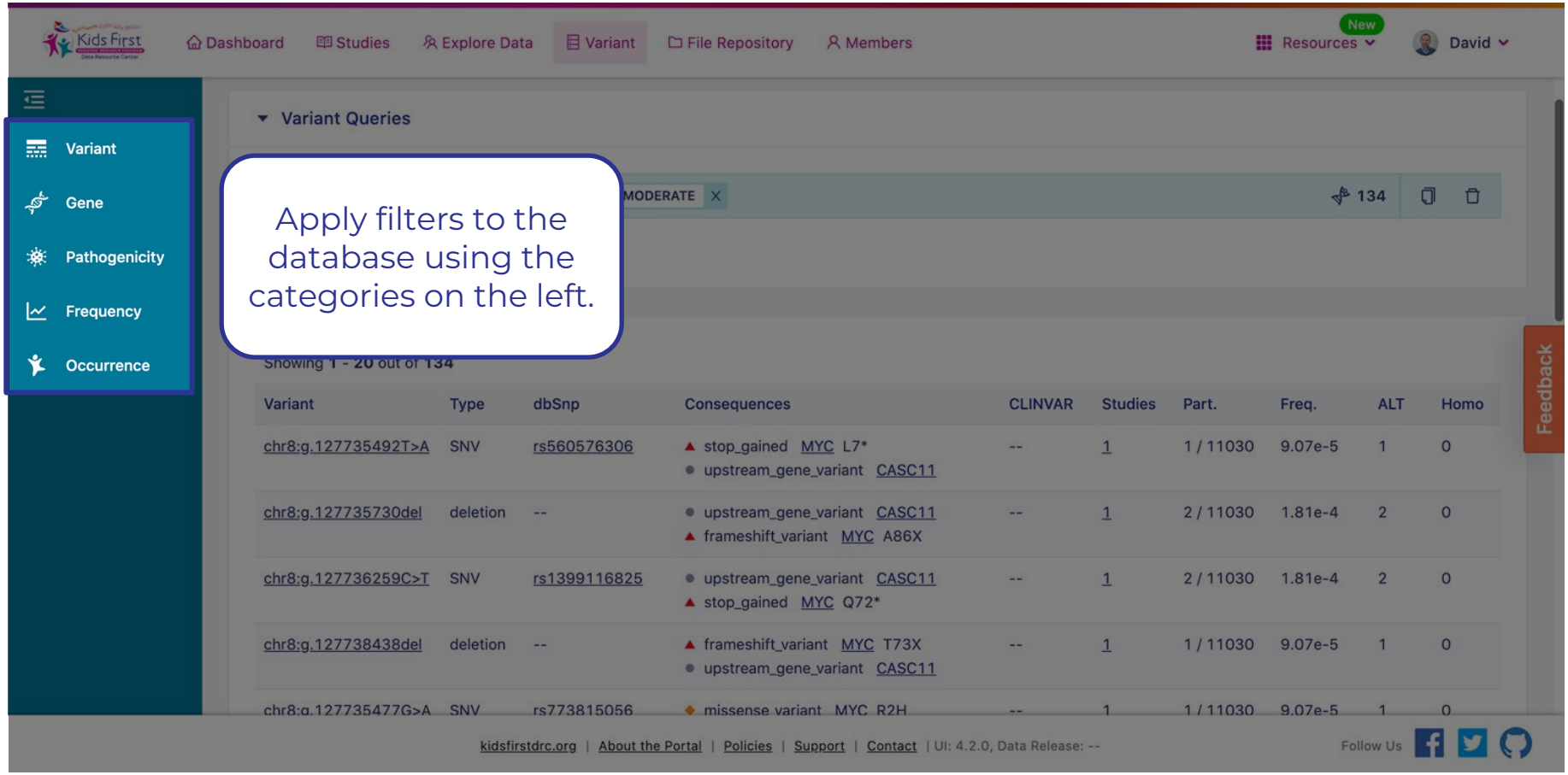
Kids First Variant Search Tool



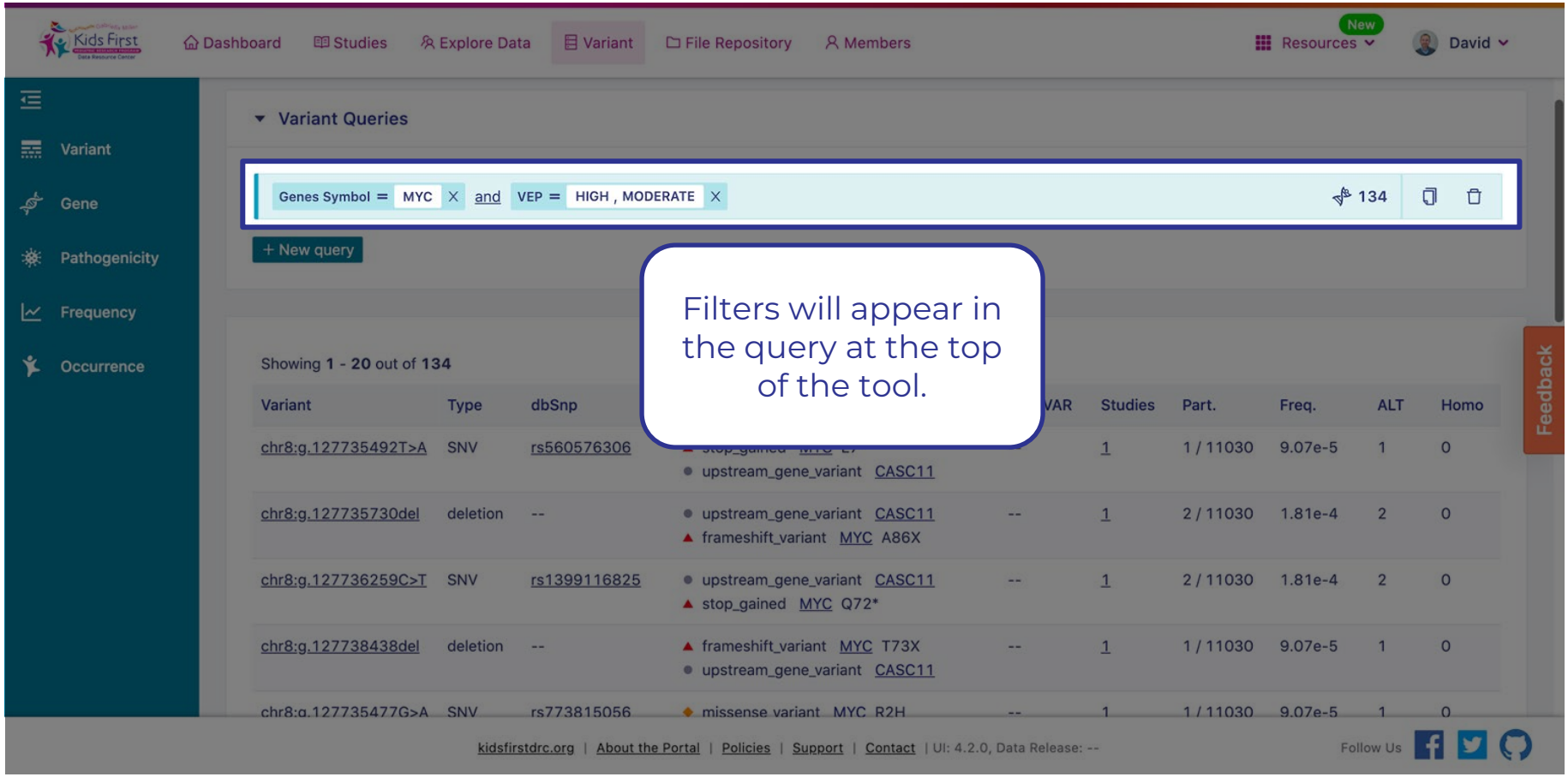
Kids First Variant Search Tool



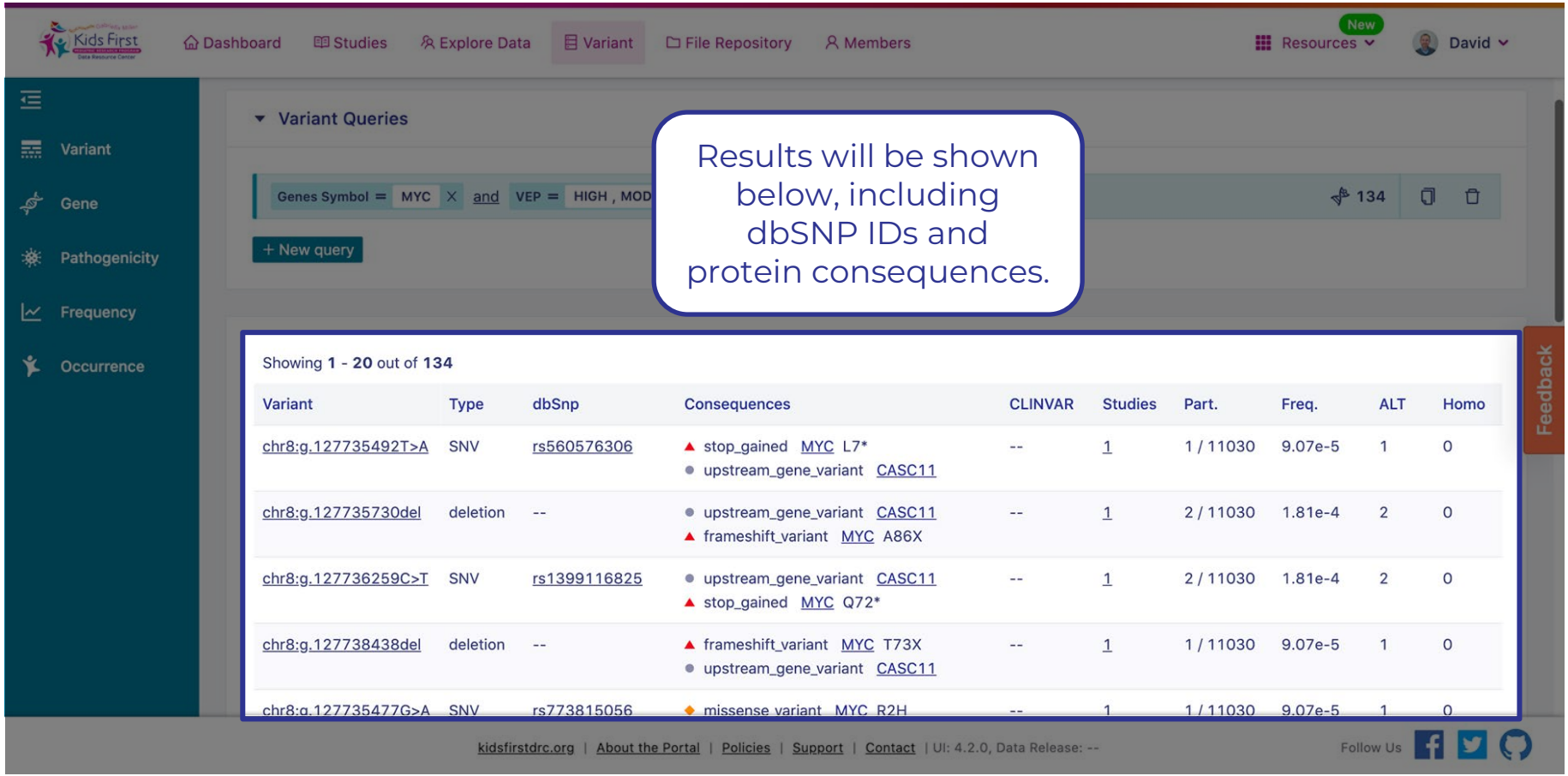
Kids First Variant Search Tool



Kids First Variant Search Tool



Kids First Variant Search Tool



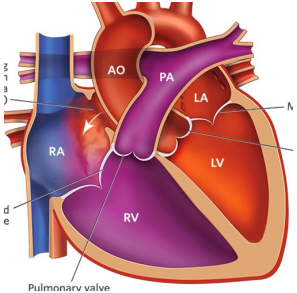
Using the Kids First Variant Search Tool

Search an individual variant

... building on findings from Dr. Mary Marazita's group

Search a chromosomal region

- ... building on findings from Dr. Sharon Diskin's group



Search based on disease-associated genes

- ... novel discovery leveraging the power of Kids First datasets.

Orofacial Clefts

- Cleft lip and cleft palate are among the most common birth defects worldwide.
- Genome-wide association studies (GWAS) can be used to identify variations more likely to be present in individuals with an orofacial cleft.

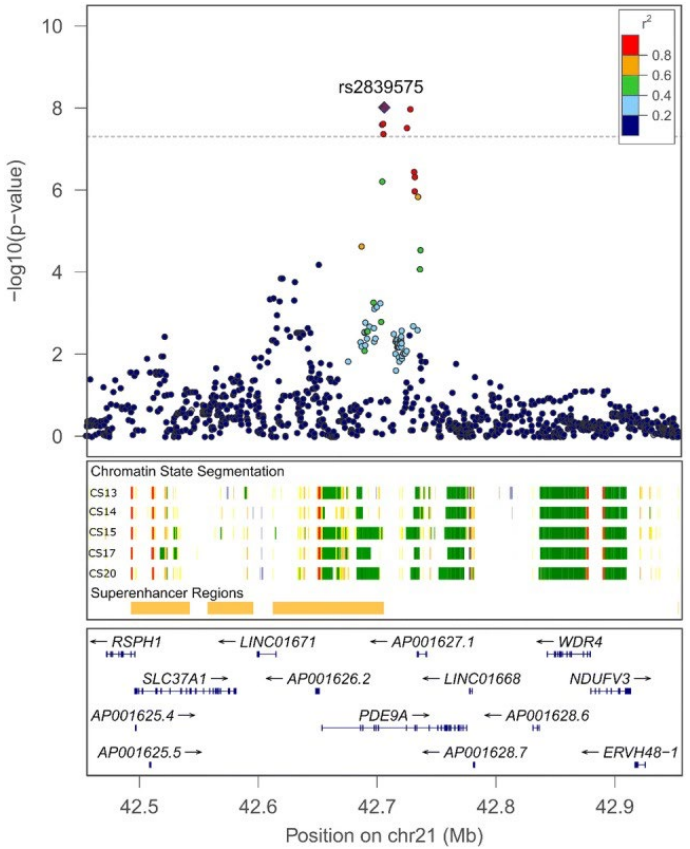
A child with a unilateral, complete cleft lip.

(Image: chop.edu)

Orofacial Clefts

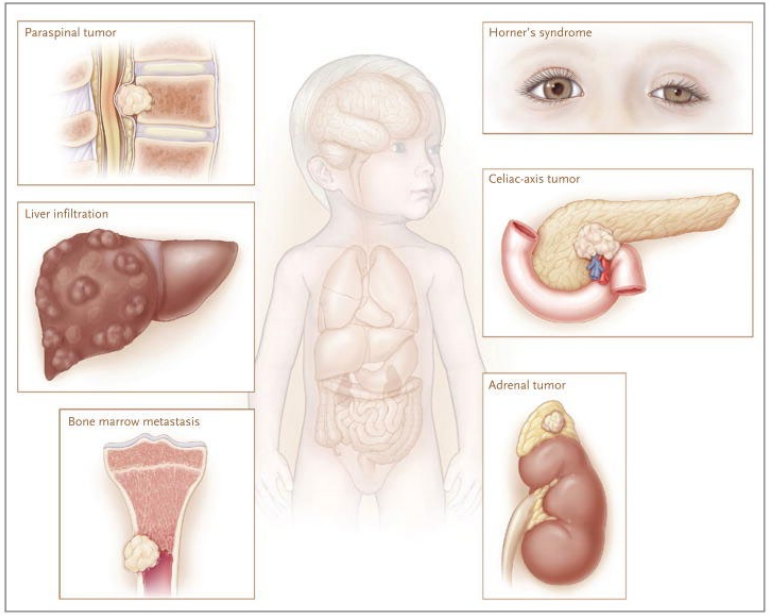
- A 2020 study using Gabriella Miller Kids First sequencing data identified a region on chromosome 21 from a population of patients from Colombia associated with orofacial cleft.

Is this variant present in participants in other Kids First studies?



(Mukhopadhyay et al., 2020)

Neuroblastoma

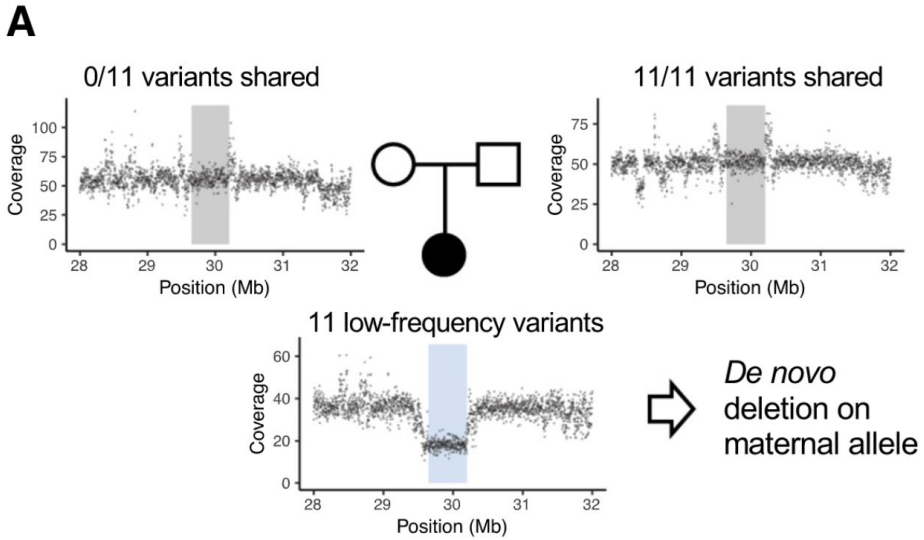


Clinical presentation of neuroblastoma.

- **Neuroblasts** are a type of cell found in unborn children which mature into neurons.
- In some children, neuroblasts continue to grow uncontrolled, forming tumors. This cancer type is called **neuroblastoma**.
- Neuroblastomas most frequently arise in adrenal glands but can be found in other tissues as well.

(Image: John M. Maris, 2010)

Neuroblastoma

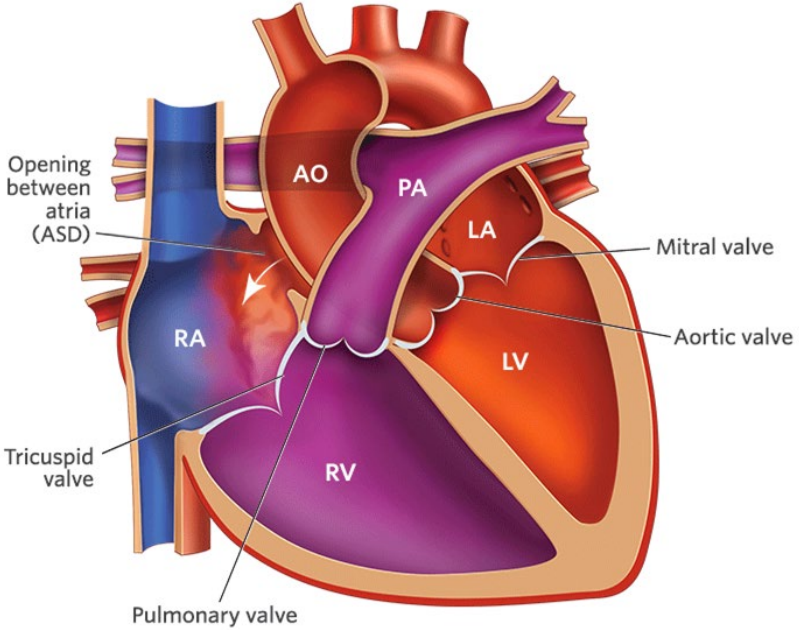


- A small deletion on chromosome 16 was found to be more frequently observed in patients with neuroblastoma.
- Kids First sequencing data identified these deletions frequently occurred spontaneously.

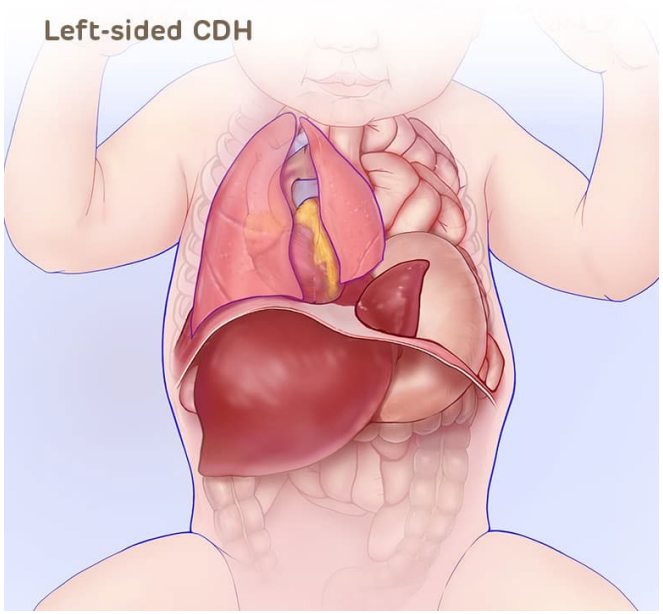
What variants from other Kids First studies are in this region?

(Egolf et al., 2019)

Congenital Heart Defects & Diaphragmatic Hernias



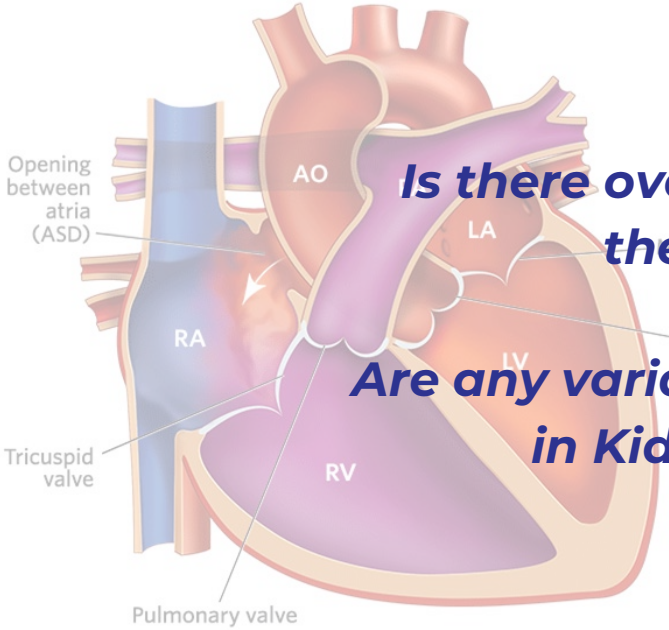
An atrial septal defect allows blood to move from the left atrium to the right atrium.



A diaphragmatic hernia allows organs such as the liver to develop out of place.

(Images: CHOP)

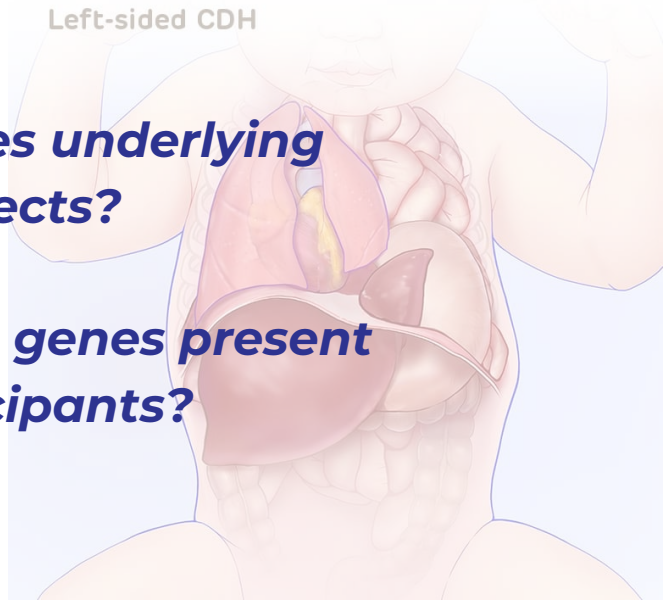
Congenital Heart Defects & Diaphragmatic Hernias



An atrial septal defect allows blood to move from the left atrium to the right atrium.

Is there overlap in genes underlying these birth defects?

Are any variants in these genes present in Kids First participants?



A diaphragmatic hernia allows organs such as the liver to develop out of place.

(Images: CHOP)

Want to learn more about Kids First platforms and data?

Valerie Cotton

Deputy Director of Data Science and Sharing

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Valerie A. Cotton @ValerieACotton

Kids First Cloud Credits Pilot Announcement

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

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.

The Kids First Community is Growing!

X01 Childhood Cancer & Structural Birth Defects Cohorts

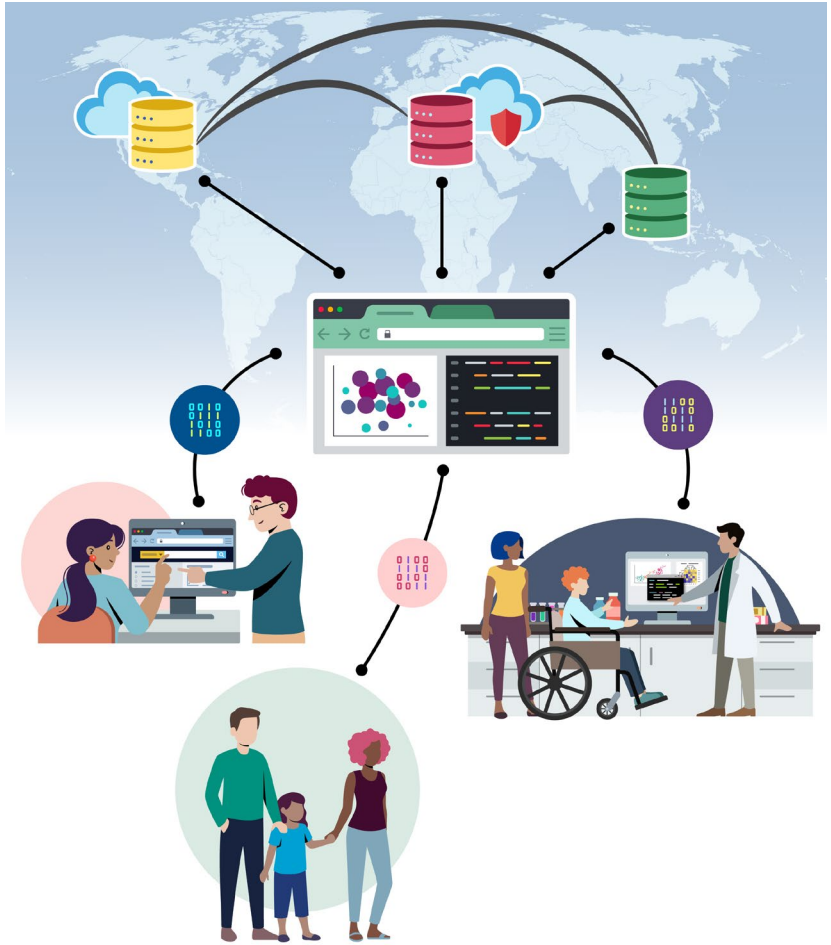
Kids First Sequencing Centers

Gabriella Miller Kids First
PEDIATRIC RESEARCH PROGRAM
Data Resource Center

Key Principle:

Invite a diversity of researchers, developers, and other community members to contribute tools, data, resources, and knowledge to the Kids First ecosystem.

You are part of Kids First!



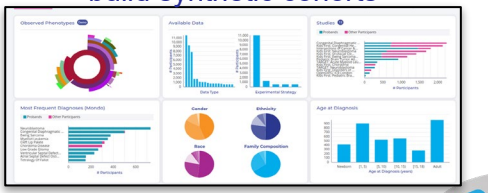
RFA-RM-22-006
Expert-Driven Small Projects to Strengthen Gabriella Miller Kids First Discovery (R03)

1. Collecting, extracting, submitting deeper data or new data types associated with Kids First datasets
2. Harmonizing or processing data to promote cross-disease or cross-species (or cross-dataset analysis)
3. Port analysis workflows to deploy within the Kids First Data Resource (e.g., CAVATICA)
4. Creating or integrating, a new or separate tool to federate with the Kids First Data Resource
5. Consenting for broader data sharing

The Kids First Data Resource for Collaborative Discovery

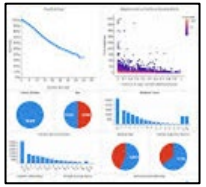
Data Resource Portal

Entry point, query/search/discover & build synthetic cohorts



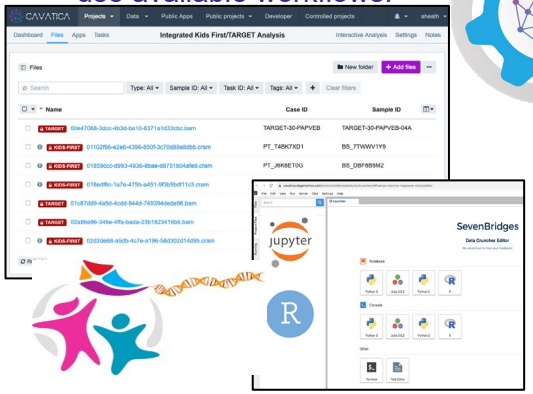
Knowledge Base Integrations (PedcBioPortal)

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 i
FHIR-based data services for semantic interoperability and coordination

Framework Services

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

GEN3 DATA COMMONS

STRIDES

Researcher challenges to data and compute

~~Current State~~		~~Future State~~ Now!
LapTop or On Premise	→	Cloud Environment CAVATICA (Platform as a Service)
Shell Based Workflow	→	Community based Standard Workflow Language
Downloading Data	→	Computational Analysis on a platform where the data lives
Not sustainable	→	Sustainable

Lessons Learned from Early Cloud Pilots

- Early pilots: Open only to Kids First X01 investigators
- Lessons learned:
  - Benefits (positive experiences)
  - Challenges & solutions

Nara Sobreira

Johns Hopkins University

Research Focus: Cartilage tumors and vascular anomalies

VIEW PROFILE >

Sharon Plon

Baylor College of Medicine

Research Focus: Identifying novel cancer susceptibility mutations

VIEW PROFILE >

Mary Marazita

University of Pittsburgh

Research Focus: Human Genetics of Complex Traits

VIEW PROFILE >

Christine Seidman

President and Fellows of Harvard College

Research Focus: Genetic Basis of Structural Heart and other birth defects

VIEW PROFILE >

Jonathan Rios

UT Southwestern Medical Center

Research Focus: Genomics of orthopaedic disease program

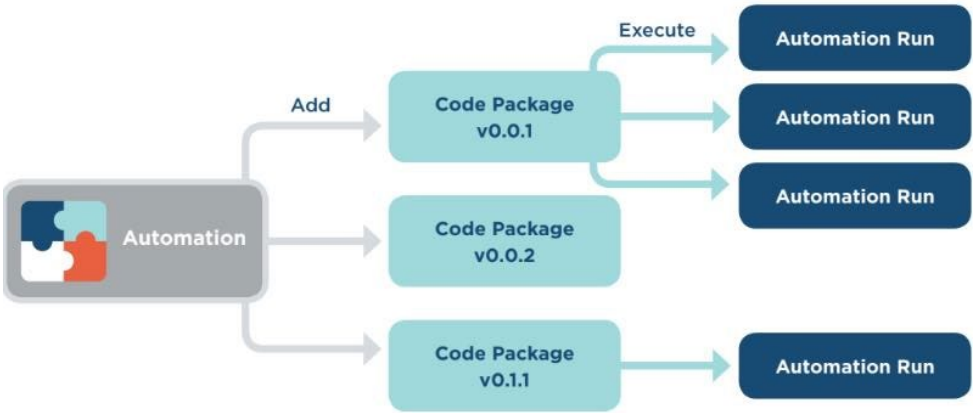
VIEW PROFILE >

Benefits: Lowers the barrier to using the cloud

- Speed of approval - did not have to wait full grant cycle
  - Request approved by NIH within 4 weeks
  - Quick set up of Cavatica billing group – connected to funds provided through STRIDES
- Safety net for getting started
  - Able to get comfortable with the Cavatica environment without consuming other resources
- Generate preliminary data for NIH grant applications
  - Helps with planning for more robust analysis

Benefit: Scalability

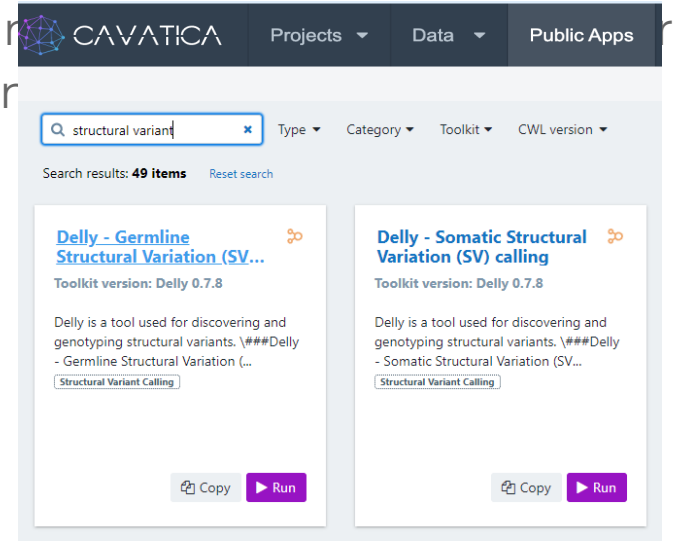
- *"the work supported by her credits that took her weeks on CAVATICA would have taken her months to do at her institution"*
- CAVATICA enables researchers to activate dozens of machines rapidly to support multiple tasks/runs at a time



Benefit: Ability to use, build & share workflows

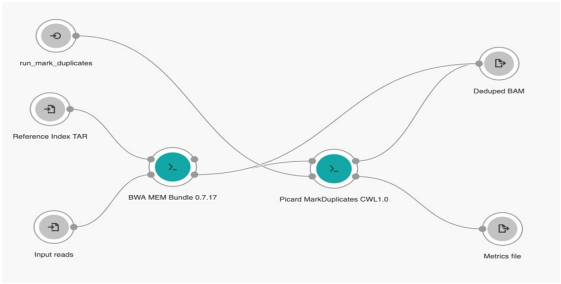
Structural Variant Calling

- Run multiple pipelines already available, tune them, and build and share a new pipeline
- Expar ructural variar



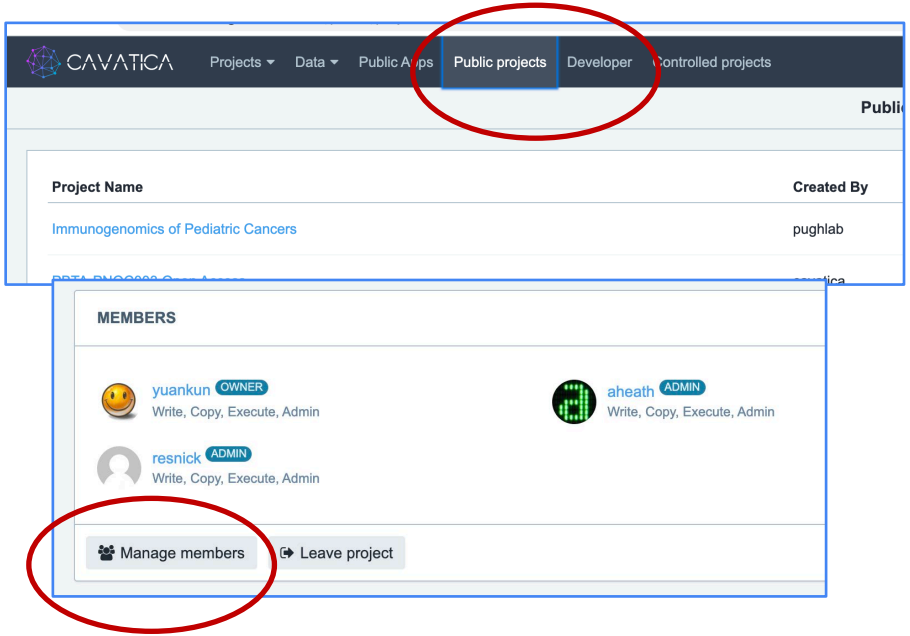
Owen Hirschi
Baylor College of Medicine

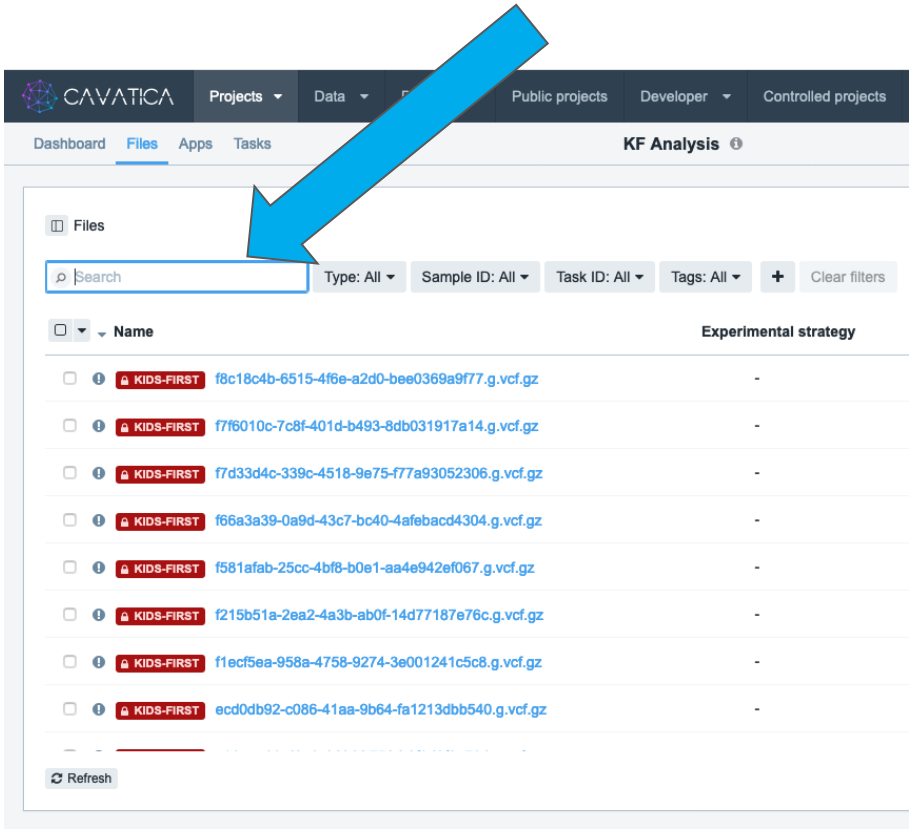
Presented at
Fall Kids First Fall 2020 Public Webinar
and NCPI Fall 2021 Webinar



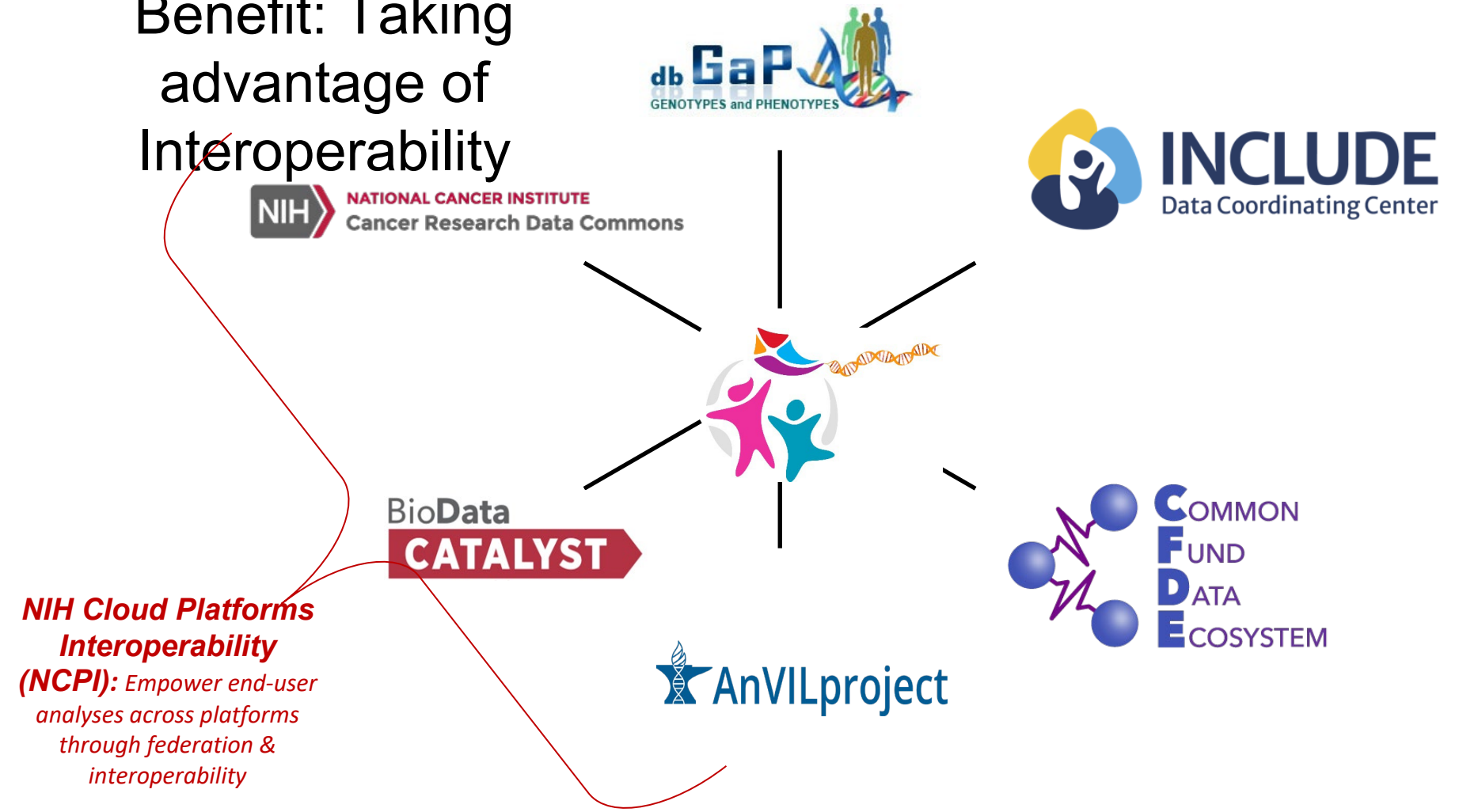
Benefit: Collaboration

CAVATICA continues to check permissions (e.g., dbGaP approval)



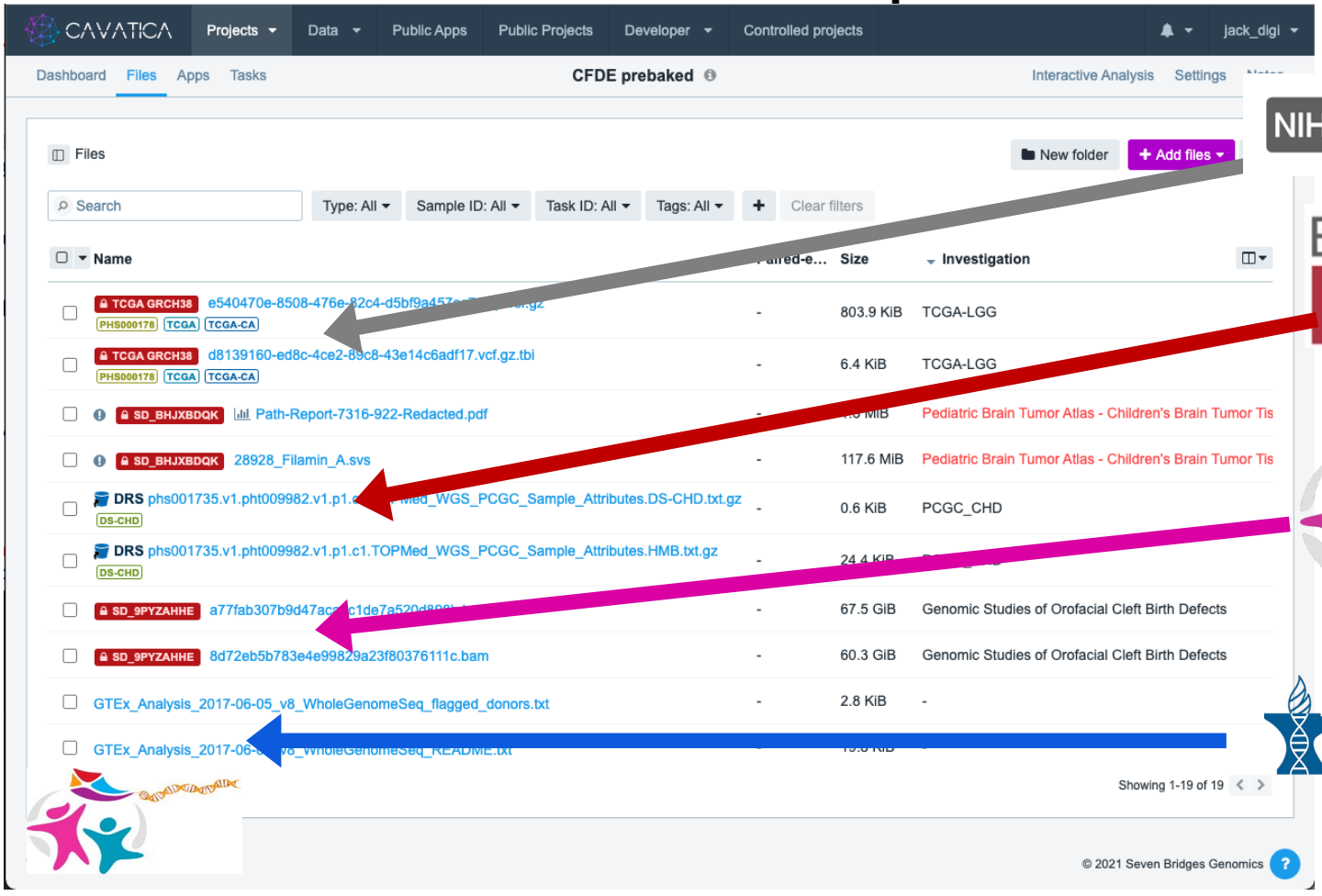


Benefit: Taking advantage of Interoperability



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

Interoperability: Kids First, TOPMed, TARGET, GTEx data all in one workspace



NIH NATIONAL CANCER INSTITUTE Cancer Research Data Commons

BioData CATALYST

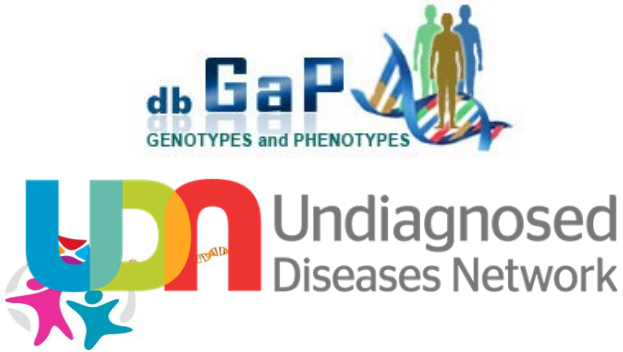
Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM Data Resource Center

AnVILproject

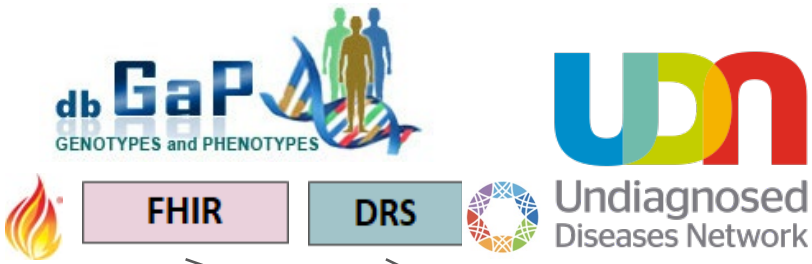
Benefit: Cloud Credits & Interoperability

What if a child represented in the Undiagnosed Disease Network had phenotypes similar to children represented in Kids First? Could you use the Kids First Data Resource to better understand the condition?

- Compare phenotypes between UDN and Kids First
- Look for overlapping genetic pathways



Analyzing "data in place"



4,000+ genomes

Up to 24,000 genomes

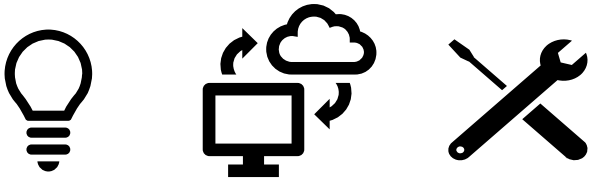
Lessons learned: Challenges & Solutions

Challenges:

- Workspace storage costs from *output files* or *uploaded data* led to over-spending
- Didn't know how to get started, concerned about costs
- Favorite tools are not in the cloud
- Not all users fully appreciated the value/scalability (especially if currently analyzing only their own dataset)

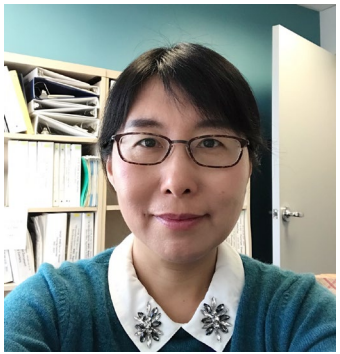
Solutions:

- New rules on closing billing groups & deleting workspaces that are overspending
- Office hours and trainings
- New ***Kids First Cloud Credits Program GitHub Page***!



Cloud Credit Requests

- Requests will be reviewed by the NIH Kids First Working Group & chaired by **Huiqing Li, NHBLI**
- Initially can request $1000
  - An additional $1000 if you describe cross-dataset analyses (Kids First + other interoperable data)
- After initial credits are spent; report on progress and request up to $5000 to continue/expand your work
  - Can apply for more if/after you share workflows/pipelines
- Inactive billing groups will be closed after 6 months; Cavatica workspaces will be deleted if they accrue costs beyond the allocation



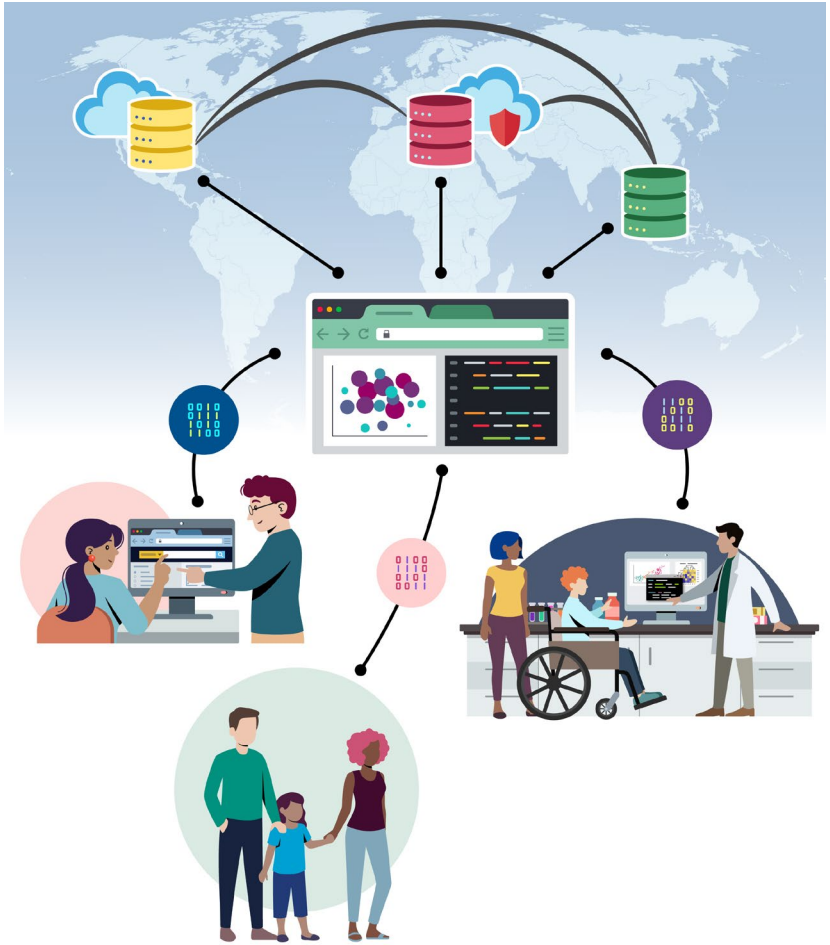
chers can continue by committing their own funds to a group

Cloud Credits: How to Apply

- **If you would like to participate in the Kids First 2022 Cloud Credits Pilot program,** please send an email to **KidsFirst@od.nih.gov** with "Kids First 2022 Cloud Credits Pilot" in the subject line, and the Working Group will follow up with additional information.

- In your email, please describe:
  - Which Kids First datasets you are interested in analyzing and whether you plan to cross-analyze Kids First data with other data.
  - Whether you have previously participated in earlier Kids First cloud credit pilots, either as an X01 or R03 investigator. In that case, please indicate whether this is a request for an additional allocation.
  - What analyses you intend to do on the CAVATICA platform

Thank you!



James Coulombe, PhD

Working Group Coordinator,
Gabriella Miller Kids First Pediatric Research Program

Chief, **Developmental Biology and Structural Variation Branch**

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Relevant NIH Mechanisms to Support Research Using Kids First Data & Resources

Scientific 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.

Kids First Program Addresses Genomic Studies for Pediatric Cancer and Structural Birth Defects

- **Grow a data resource in the cloud** to accelerate pediatric cancer and structural birth defects research leading to better prevention, diagnosis, and treatments for patients and families
  - FAIR Data
  - Data sharing
  - Data analysis and visualization
  - Collaborative research

Public Law 113–94 113th Congress

SEC. 1 This Act may be cited as the ‘‘Gabriella Miller Kids First Research Act’’.

SEC. 3. 10–YEAR PEDIATRIC RESEARCH INITIATIVE. SUPPLEMENT, NOT SUPPLANT; PROHIBITION AGAINST TRANSFER.

Funds appropriated pursuant to section 402A(a)(2) of the Public Health Service Act, as added by subsection (b)— (1) shall be used to supplement, not supplant, the funds otherwise allocated by the National Institutes of Health for pediatric research; and (2) notwithstanding any transfer authority in any appropriation Act, shall not be used for any purpose other than allocating funds for making grants as described in section 402(b)(7)(B)(ii) of the Public Health Service Act, as added by subsection (a). Approved April 3, 2

Small Research Grants for Analyses of Gabriella Miller Kids First Pediatric Research Data

- Program Announcement with Referral (PAR)
- R03 small grant mechanism
  - Awards for up to 2 years
  - Budget expanded up to $100,000/year in direct costs
  - Preliminary data is not required
- Past FOAs:PAR-16-348, PAR-18-733, PAR-19-069, PAR-19-375
  - 97 applications received
  - 24 received funding
  - PAR-19-375 Application dates until October/November 16th, 2022

Expert-Driven Small Projects to Strengthen Gabriella Miller Kids First Discovery (R03 Clinical Trial Not Allowed)

Awards for up to 2 years
Budget expanded up to $100,000/year in direct costs
Preliminary data is not required

- RFA-RM-21-011
  - Eleven applications received
  - 6 Funded (one through the INCLUDE program)

- RFA-RM-22-006
  - Applications due June 10th, 2022

Investigator Initiated “Parent” FOAs

R01:
PA-20-185 NIH Small Research Grant Program (Parent R03 Clinical Trial Not Allowed)

R03:
PA-20-200 NIH Small Research Grant Program (Parent R03 Clinical Trial Not Allowed)

R21:
PA-20-195 NIH Exploratory/Developmental Research Grant Program (Parent R21 Clinical Trial Not Allowed)

NIH Funding Opportunities

Go shopping:
https://grants.nih.gov/funding/searchguide/index.html#/

- R01: PAR-21-229: Screening and Functional Validation of Human Birth Defects Genomic Variants (R01 Clinical Trial Not Allowed)

- R21: RFA-CA-22-02: Development of Innovative Informatics Methods and Algorithms for Cancer Research and Management (R21 Clinical Trial Optional)

- R21: PAR-20-078: Secondary Analysis of Existing Datasets in Heart, Lung, and Blood Diseases and Sleep Disorders (R21 Clinical Trial Not Allowed)

Questions?

Thank you!