Pre-Application Webinar for

**PAR-18-583, 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)**

February 8th, 2018
3:00 pm EST
Background

• Initiated in response to the 2014 Gabriella Miller Kids First Research Act
  – Signed into law on April 3, 2014
  – Ended taxpayer contribution to presidential nominating conventions
  – Transferred $126 million into the Pediatric Research Initiative Fund
  – Authorized appropriation of $12.6 million per year for 10 years to the NIH Common Fund 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.
Kids First Working Group

• Kids First is a trans-NIH effort supported by the NIH Common Fund
• Institutes that chair the Kids First Working Group: NICHD, NHLBI, NCI, NHGRI
• Other Institutes that are part of the Working Group: NIDCR, NIDCD, NIDA, NIAAA, NIDDK, NIEHS, NEI, NIAMS, NIAID, ORIP, and the CDC

For full list of members: https://commonfund.nih.gov/kidsfirst/members
Kids First Leadership Team

Program Officers

James Coulombe (NICHD)
Working Group Coordinator
Sequencing Centers Project Officer

Danielle Daee (NCI)
Sequencing Center Project Scientist

Jaime Guidry Auvil (NCI)
Sequencing Center Project Scientist

Malcolm Smith (NCI)

Adam Felsenfeld (NHGRI)

Lu Wang (NHGRI)

Jonathan Kaltman (NHLBI)

Maarten Leerkes (NHLBI)
Data Resource Project Scientist

Charlene Schramm (NHLBI)
Data Resource Program Officer

Point-of-Contact

Valerie Cotton (NICHD)
Program Manager

Common Fund, OD

Marie Nierras – Program Leader
Danyelle Winchester – Policy, Planning,
Evaluation, and Communications
Michael Steenstra – Operations and Budget

Grants Management

Bonnie Jackson (NICHD)

Tracee Foster (NHLBI)
Kids First Major Initiatives

1. Cohort identification and DNA sequencing
   - Identify children with childhood cancer and/or structural birth defects, and their families, PAR-15-259; PAR-16-150; PAR-17-063; PAR-18-583
   - Whole genome sequencing by the Kids First Sequencing Centers, RFA-RM-16-001

2. Gabriella Miller Kids First Pediatric Data Resource, RFA-RM-16-010
   - Will develop a resource where the pediatric research community can access well-curated clinical and genetic sequence data that will allow them to identify genetic pathways that underlie childhood cancer and structural birth defects.

3. Data Analysis: Data Mining & Demonstration Projects [future]
   - Support analysis of Kids First-generated and non-Kids First-generated data to uncover new insights into the biology of childhood cancer and structural birth defects, including the discovery of shared genetic pathways between childhood cancer and structural birth defects
X01 mechanism

• Not an “award”; recipients are selected for the opportunity to have their cohort sequenced

• No Notice of Award; Kids First can provide a letter acknowledging and explaining that your project was selected for our X01 program

• Not listed in the NIH RePORTER
  – Abstracts and X01 information listed on Kids First website: https://commonfund.nih.gov/kidsfirst/fundedresearch

• No funds, but can apply for R01s or R03 to support analysis of X01 project:
  PAR-16-348: Small Research Grants for Analyses of Data for the Gabriella Miller Kids First Data Resource (R03)
  Note: this FOA will be reissued in time for Cycle II standard receipt dates
X01: Fourth Cycle

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. FY 2015: PAR-15-259
   • 2 childhood cancer cohorts
   • 5 structural birth defects cohorts

2. FY 2016: PAR-16-150
   • 3 childhood cancer cohorts
   • 5 structural birth defects cohorts

3. FY 2017: PAR-17-063
   • 2 childhood cancer cohorts
   • 5 structural birth defects cohorts
   • 1 cohort with overlap of structural birth defects and childhood cancer

4. FY 2018: PAR-18-583

Kids First plans to continue sequencing for three more years, provided that cohorts are available and funds are appropriated
Kids First X01 Cohorts

Adolescent Idiopathic Scoliosis (FY16)
Cancer Susceptibility (FY16)
Congenital Diaphragmatic Hernia (FY15, 16, 17)
Craniofacial Microsomia (FY17)
Disorders of Sex Development (FY15)
Enchondromatoses (FY17)
Ewing Sarcoma (FY15, 17)
Familial Leukemia (FY16)
Hearing Loss (FY16)
Infantile Hemangiomas (FY17)
Neuroblastomas (FY16)
Nonsyndromic Craniosynostosis (FY17)
Orofacial Clefts; Caucasian (FY15), Latin American (FY16), Asian & African (FY17)
Osteosarcoma (FY15)
Patients with both childhood cancer and birth defects (FY17)
Structural Heart & Other Defects (FY15, 16)
Syndromic Cranial Dysinnervation Disorders (FY15)
Sequencing Centers

**HudsonAlpha Institute for Biotechnology**
- Shawn Levy, Ph.D, Director of the Genomic Services Lab

**St. Jude Children’s Research Hospital**
- Jinghui Zhang, Ph.D.
- John Easton, Ph.D.

**Broad Institute of MIT & Harvard**
- Stacey Gabriel, Ph.D., Senior Director, Genomics Platform
- Michael Talkowski, Ph.D.
- Daniel MacArthur, Ph.D.

RFA-RM-16-001
Sequencing Centers

Perform sequencing & variant calling for X01 cohorts

• **Germline/Normal**: Standard WGS at 30X coverage
• **Tumor or Affected tissue (when available)**: 30X WGS + 100X WES + 100X RNASeq
Kids First Data Resource Center

Goal: accelerate discovery of genetic etiology and shared biologic pathways by building a collection of curated genomic and phenotypic data from Kids First X01 projects and providing a central portal where these data and analysis tools will be readily accessible to the research community

• Charged with re-processing and “harmonizing” data generated by the sequencing centers to facilitate analyses across all Kids First datasets

Phenotype data $\rightarrow$ Sequence data $\rightarrow$ Kids First DRC $\rightarrow$ X01 Recipients $\rightarrow$ Pediatric Research Community

X01 investigators are encouraged to utilize and work collaboratively with the Kids First Data Resource Center to pursue specific analyses. Visit: kidsfirstdrc.org
Investigators at the Center for Data Driven Discovery in Biomedicine (D3b) at Children’s Hospital of Philadelphia will lead the joint effort to develop the Kids First Data Resource Center with Seven Bridges Genomics, Inc., the Ontario Institute for Cancer Research, the University of Chicago, Children’s National Health System and the Oregon Health and Science University.

• PI: Adam Resnick
PAR-18-583
Goals & Expectations

Visit X01 FAQs:
https://commonfund.nih.gov/kidsfirst/faq
Sequencing

**Goal:** Generate high-quality Whole Genome Sequence data, as well as whole exome and transcriptome for tumors/affected tissue, to discover genetic variants contributing to pediatric conditions

**Expectations:**
DNA extractions must be of sufficient quality and concentration for WGS (and WES).
RNA extractions (for tumor/affected tissue) must be of sufficient quality and concentration for RNASEq.
Sequencing

Sequencing Centers perform sequencing & variant calling
Generate CRAM/BAM, FASTQ (RNA), & VCF files

• **Germline/Normal**: Standard WGS at 30X coverage
• **Tumor or Affected tissue (when available)**: 30X WGS + 100X WES + 100X RNASEq

You may propose other approaches (e.g., linked long read/phased genomes, higher coverage) in your application; however, project design will be finalized in discussions among the X01 investigators, the sequencing centers, and NIH program staff
Volume/Concentration Recommendations

Can be found on our FAQ page: [https://commonfund.nih.gov/kidsfirst/FAQ](https://commonfund.nih.gov/kidsfirst/FAQ)

<table>
<thead>
<tr>
<th>Amount of DNA/RNA and coverage</th>
<th>Concentration</th>
<th>Coverage</th>
<th>Additional info.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WGS</strong></td>
<td>~2ug DNA</td>
<td>20-50 ng/ul preferred</td>
<td>30X</td>
</tr>
<tr>
<td><strong>WES</strong></td>
<td>275 ng DNA (minimum); 1 ug recommended</td>
<td>20 ng/ul (minimum)</td>
<td>100X, greater than 80% coding exons covered at 20X</td>
</tr>
<tr>
<td><strong>RNA-Seq</strong></td>
<td>750 ng total RNA (minimum); 1 ug recommended</td>
<td>20 ng/ul (minimum)</td>
<td>100X, greater than 40% coding exons covered at 20X</td>
</tr>
</tbody>
</table>
Data Sharing

**Goals:**
1. Make data generated by Kids First as accessible as possible to the research community.
2. Enable researchers to easily combine/compare datasets for cross-dataset analyses.

**Expectations:**
- Cohort participants must have given consent to allow sharing of individual-level sequence and relevant phenotype data through an NIH-approved repository (e.g. dbGaP)
- Samples that are consented for broadest level of data sharing (i.e. for general research use) are of highest priority

*See below or visit [Kids First Data Sharing FAQs](#) for more information*
Six Month Pre-Release Period

X01s investigators have six (6) months of proprietary access to the data before it is made available to the public. They can work with the Kids First sequencing centers, the DRC, and other direct collaborators during the “pre-release period”.

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### Pre-release Analyses

- 0-6 months
  - X01 PIs & Collaborators (including Kids First Sequencing Centers & DRC)

### Public Release

- 6+ months
  - Pediatric Research Community (request access via dbGaP)

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Clinical/Phenotype Data

**Goal:** Well-phenotyped data helps inform analyses and how pathways/conditions overlap. The DRC will leverage existing community standards to harmonize clinical/phenotype data which facilitates searching, analysis, and interoperability with other data efforts.

**Expectations:**
- Basic data elements are expected and deep phenotyping is preferred.
- Describe what clinical/phenotype information is available for submission to the Kids First DRC (see “Other Attachments”) and whether participants can be re-contacted.
Study Design

**Goal**: Study design, sample size, and family structures are sufficient to lead to genetic discovery

**Expectations**:

- Large sample sizes preferred
  - Consider collaborating with other investigators to pool samples together
- Non-trios: describe the number of probands and affected/unaffected family members proposed for sequencing
Analysis Plans

**Goal:** Have investigators demonstrate that the proposed project has an adequate research design for genetic discovery, and that the X01 applicants are prepared to perform these analyses

**Expectations:**
- While Kids First recognizes that analytical power will increase when the data from each individual study is incorporated with other data that will be part of the Data Resource, it is important to demonstrate that the data will be useable on its own.
- Consider partnering with other research teams with relevant expertise to develop the analysis plan.
Program Balance

**Goal**: Broaden the diversity of both childhood cancer and structural birth defects datasets that are represented in the Data Resource.

**Expectation**: Priority may be given to cohorts with conditions not previously sequenced under Kids First (if many applications score well during peer review).
Other Attachments

1) Institutional Certification (or provisional certification with description of data use limitations)
2) Sample Information
3) Clinical/Phenotype Data
4) Family Structure (Optional)
Other Attachments: Institutional Certification

Provide an institutional certification (or provisional certification) that...

– covers all sites contributing samples to your project
– specifies whether data is consented for deposition in dbGaP or other NIH-approved repositories
– indicates the data use limitations (DULs) and data use limitation modifiers (see example DULs below)

<table>
<thead>
<tr>
<th>Collaborating Site Name</th>
<th>Data Use Limitation</th>
<th>Data Use Limitation Modifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eg: Cold Cohort Study</td>
<td>Health/Medical/Biomedical</td>
<td>IRB, PUB, COL, NPU, MDS, GSO</td>
</tr>
<tr>
<td>Eg: Cold Cohort Study</td>
<td>Disease Specific Research [Lung Cancer]</td>
<td>IRB, PUB, COL, NPU, MDS, GSO</td>
</tr>
</tbody>
</table>
Institutional Certification Steps

1) Download the current NIH Institutional Certification template: https://osp.od.nih.gov/scientific-sharing/institutional-certifications/

2) Fill out the first page, include all sites contributing samples for sequencing. 
   Leave the second page blank for the IRB to fill out.

3) Provide the Institutional Certification to the IRB along with the participant consent forms for each site and any other pertinent information (e.g. protocols).

4) The IRB reviews the consent form(s) to determine whether there are any data use limitations (DULs) and/or DUL modifiers for each site or “consent group”.

   “General Research Use” is expected, unless specific uses are clearly prohibited.

5) After IRB review, the Institutional Certification is signed by the appropriate officials (third page) and submitted to NIH.

A cover letter that outlines these steps is available for download for you and your IRB

List all sites contributing samples

All Kids First genomic data (e.g., BAMs, VCFs) are “controlled-access”

We encourage checking both “alleles” and “frequencies” (unless prohibited)
Extramural Institutional Certification

For guidance on drafting data use limitations, please refer to the NIH Points to Consider in Drafting Effective Data Use Limitation Statements found at: [http://gds.nih.gov/pdf/nih_prc_in_drawing_dul_statements.pdf](http://gds.nih.gov/pdf/nih_prc_in_drawing_dul_statements.pdf). Data use limitations are developed based on the original informed consent from the participant.

<table>
<thead>
<tr>
<th>Data Use Limitations (will be used in dbGaP to create Consent Groups)</th>
<th>GRU</th>
<th>Use of the data is limited only by the terms of the Data Use Certification; these data will be added to the dbGaP Collection.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health/Medical/Biomedical</td>
<td>HMB</td>
<td>Use of the data is limited to health/medical/biomedical purposes, does not include the study of population origins or ancestry.</td>
</tr>
<tr>
<td>Disease-specific [list disease]</td>
<td>DS</td>
<td>Use of the data must be related to the specified disease.</td>
</tr>
<tr>
<td>Other</td>
<td>[ENTER CUSTOMIZED TEXT, IF APPLICABLE]</td>
<td></td>
</tr>
</tbody>
</table>

Data Use Limitation Modifiers

| IRB approval required | PUB | Requestor must provide documentation of local IRB approval. |
| Publication required | PUB | Requestor agrees to make results of studies using the data available to the larger scientific community. |
| Collaboration required | COL | Requestor must provide a letter of collaboration with the primary study investigator(s). |
| Not-for-profit use only | NPU | Use of the data is limited to not-for-profit organizations. |
| Methods | MDS | Use of the data includes methods development research (e.g., development of software or algorithms) |
| Genetic studies only | GSO | Use of the data is limited to genetic studies only. |

Using the tables above, please indicate in the form below the consent group(s) for each collaborating study site. Use one row per consent group.

<table>
<thead>
<tr>
<th>Site/University #1</th>
<th>Data Use Limitation</th>
<th>Data Use Limitation Modifiers</th>
<th>Site/University #2</th>
<th>Data Use Limitation</th>
<th>Data Use Limitation Modifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eg: Cold Cohort Study</strong></td>
<td>Health/Medical/Biomedical</td>
<td>IRB</td>
<td><strong>[Site/University #1]</strong></td>
<td>General Research Use</td>
<td>IRB</td>
</tr>
<tr>
<td><strong>Eg: Cold Cohort Study</strong></td>
<td>Disease Specific Research [Lung Cancer]</td>
<td>IRB</td>
<td><strong>[Site/University #1]</strong></td>
<td>General Research Use</td>
<td>IRB</td>
</tr>
</tbody>
</table>

Select consent group title...
1) **Provisional Certification: Data Sharing and Data Use Limitations**

If you provided a Provisional Institutional Certification, because you are unable to provide a full Institutional Certification, please describe the anticipated data use limitations based on the language of the consent form(s) signed by the participants in the proposed cohort. For a list of standard DULs and modifiers, please review the Institutional Certification template: [https://osp.od.nih.gov/scientific-sharing/institutional-certifications](https://osp.od.nih.gov/scientific-sharing/institutional-certifications) or [https://osp.od.nih.gov/wp-content/uploads/standard_data_use_limitations.pdf](https://osp.od.nih.gov/wp-content/uploads/standard_data_use_limitations.pdf).

<table>
<thead>
<tr>
<th>Site</th>
<th><strong>Data Use Limitation</strong> (GRU, HMB, DS)</th>
<th><strong>Data Use Limitation Modifiers</strong> (IRB, PUB, COL, NPU, MDS, GSO)</th>
</tr>
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</table>
2) **Sample Information: Sample Sources and Details.** Please edit and fill-in the table below to describe the DNA (and RNA, for tumors and/or affected tissue) samples that you propose for sequencing.

**Total Number of Samples proposed for sequencing:**

<table>
<thead>
<tr>
<th>DNA (and RNA) source</th>
<th>Number of Samples</th>
<th>Extraction Method</th>
<th>Concentration</th>
<th>Quality (Metric used: ___)</th>
<th>Method of Quantitation</th>
<th>Number of Samples Ready to Ship by August 2018</th>
<th>Number of Samples Ready to Ship by January 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saliva or Buccal swab</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>[other tissue, edit here to describe]</td>
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<td></td>
</tr>
</tbody>
</table>

**Tumors or Affected Somatic Tissue**

| DNA – Frozen Tissue | | | | | | | |
| RNA – Frozen Tissue | | | | | | | |
| DNA – Embedded Tissue | | | | | | | |
| RNA – Embedded Tissue | | | | | | | |

**Total**
Other Attachments: Fillable Form

Phenotype Information & Demographics

Available Phenotype or Clinical Information (for #3 Phenotype Data). Please edit or add to the table below to indicate what phenotype information is available for the case/proband, parents, and/or other family members. The information you list is intended to be shared through the Kids First Data Resource.

<table>
<thead>
<tr>
<th>Demographic</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Other age information (age at specimen collection, age at death etc....)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td></td>
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<tr>
<td>List any other demographic information:</td>
<td></td>
</tr>
</tbody>
</table>

Clinical information (e.g., type of birth defect, primary tumor site)

List the variables:

Other phenotypic information (e.g., other phenotypic measurements that may be related to the primary outcome)

List the variables:

Family medical history (e.g., family history of birth defects, family history of cancer)

List the variables:
Other Attachments: Pedigree or Table

Describe Family structures (proband-parent dyads, proband-parent-sibling quads, multiplex families, consanguineous families)

- How many samples per family? How many are affected/unaffected?

<table>
<thead>
<tr>
<th>Family type</th>
<th>Number of families</th>
<th>Total Germline Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband/Child + Parents (unaffected) Trios</td>
<td>XX</td>
<td>XX affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XX unaffected</td>
</tr>
<tr>
<td>Proband + 1 affected FDR + [Unaffected FDRs]</td>
<td>XX</td>
<td>XX affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XX unaffected</td>
</tr>
<tr>
<td>Proband + 2 affected FDR + [Unaffected FDRs]</td>
<td>XX</td>
<td>XX affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XX unaffected</td>
</tr>
<tr>
<td>Total</td>
<td>XXX</td>
<td>XXX</td>
</tr>
</tbody>
</table>

FDR= First Degree Relative
2018 X01 Timeline

Jan 16 – Published X01 FOA

Feb 8 – Webinar for X01 applicants

Feb 22 – X01 Letters of Intent Due

Mar 22 – X01 Applications Due

April/May – NHGRI-SEP Review X01 applications

June/July – KF WG Discusses Review & Drafts Cohort Selection

July/Aug – Finalize X01 cohort decision & notify recipients

Aug/Sept – X01 cohorts enter pipeline

Winter/Spring 2018

Summer 2018

Fall 2018
Questions?

- Un-mute yourself by selecting *6 on your telephone or clicking on the mic symbol under “Audio Connection”,
- or
- Message us via the WebEx chat function
Thank You!

Email Additional Questions and Comments to the Kids First Mailbox: kidsfirst@od.nih.gov