Webinar Instructions

• Welcome to the Public Webinar for the Gabriella Miller Kids First Pediatric Research Program

• Every participant is muted upon entry. Please remain muted until the question/discussion period. You can unmute yourself by selecting *6 on your telephone or clicking on the mic symbol to the right of your user name (if you called in through the computer).

• You can ask technical questions using the chat service to the host throughout the webinar. Please save all programmatic/scientific questions for the question period. Additional program-related questions can be emailed to: KidsFirst@od.nih.gov.

This Webinar will be recorded and posted to the Kids First website. We will start at 2:00 pm.
Lorette Javois, PhD (NICHD)
Jonathan Kaltman, PhD (NHLBI)
Jaime Guidry Auvil, PhD (NCI)
Marie Nierras, PhD (Office of the Director, Common Fund)
Philip Lupo, PhD (Baylor College of Medicine)

November 18th, 2016
Before we get started...

There will be a question/answer section at the end

If you have questions or comments about the Kids First program at any point in the future, please let us know by emailing the Kids First Mailbox

kidsfirst@od.nih.gov
Presentation Outline

1. Scientific focus of Kids First Program
2. Genetic variation and DNA sequencing as it relates to the Kids First Program
3. Importance of studying cancer and birth defects together
4. Kids First Program major initiatives
5. Question and answer session
Childhood cancers and structural birth defects have profound, lifelong effects on patients and their families

• ~15,500 new cases of cancer were diagnosed among children in the U.S. in 2014. ~1,900 children died from the disease.

• One in 33 infants born in the U.S. has a birth defect. They are the leading cause of death during the first year of life and account for half of all pediatric hospitalizations.
Kids First will develop a large-scale data resource that will allow researchers everywhere access to vast amounts of childhood cancer and structural birth defects genetics data that will greatly accelerate their research.

This will facilitate new discoveries and novel ways of thinking about these conditions and is anticipated to accelerate scientific progress in pediatric research that will improve the lives of the children and families impacted by these conditions.
Kids First Major Initiatives

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

- Cohort ID & DNA Sequencing
- Kids First Data Resource
- Data Analysis

Covered in detail today in this presentation
Kids First Major Initiatives

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

- **Cohort ID & DNA Sequencing**
- **Kids First Data Resource**
- **Data Analysis**

Covered in detail during another webinar tentatively planned for March/April 2017
Why is DNA sequencing important?

Knowing which DNA changes are causing or contributing to disease/conditions helps improve diagnosis and accelerates the development of prevention, early detection, and therapeutic interventions.
DNA and Genetic variation

• Hereditary material

• Order, or sequence, of bases determines the information available for building and maintaining an organism

• All humans share 99.9% of their DNA with everybody else

• The remaining 0.1% is genetic variation and contributes to our differences
Genetic variation contributes to individual differences

• Height, eye color, blood pressure
• Most genetic variation does not cause or contribute to overt disease/conditions

• On rare occasions, genetic variation does cause or contribute to disease/conditions
Changes to the DNA sequence may contribute to disease

- When changes occur to the DNA sequence, they can cause or contribute to disease/conditions
- Knowing which DNA changes cause or contribute to disease/conditions helps researchers develop cures and treatments
How will studying genetics help lead to treatments and cures?

DNA

Proteins

Biological Pathways

Biological Function
(blood pressure, metabolism)

DNA change

Nonfunctional Protein

Altered Biological Pathway

Altered Biological Function
(diabetes, cancer, birth defect)
How will studying genetics help lead to treatments and cures?

• Knowing the DNA changes gives researchers clues to which biological pathways are causing or contributing to disease/conditions

• The majority of drugs and treatments target biological pathways
  • Knowing the pathway is an important step in drug development
Why study childhood cancer and structural birth defects together?

Philip Lupo, Ph.D.
Assistant Professor
Pediatrics-Oncology
Baylor College of Medicine
Birth Defects

• Structural or functional anomalies present at the time of birth
• “1 in 33 born with a birth defect”
Birth Defects

• Structural or functional anomalies present at the time of birth
• “1 in 33 born with a birth defect”

• 4 most common birth defects
  • Congenital heart defects
  • Neural tube defects
  • Hemoglobin disorders
  • Down syndrome

20% of all birth defects

>7,000 birth defects
Etiology of Birth Defects

• Chromosomal abnormalities
  • 6% of all birth defects
  • Ex. Down syndrome (trisomy 21)

• Single gene defects
  • 7.5% of all birth defects
  • Ex. Neurofibromatosis type I (changes in skin pigmentation & growth of tumors along nerves in the skin, brain, and other parts of the body)

• Multifactorial disorders (non-syndromic)
  • 85% of all birth defects
  • Ex. Congenital heart disease
Childhood Cancers

SEER Delay-Adjusted Incidence and US Mortality
All Childhood Cancers, Under 20 Years of Age
Both Sexes, All Races, 1975-2010

Delay-Adjusted Incidence

Mortality

Data from the Surveillance, Epidemiology, and End Results (SEER) Database
Etiology of Childhood Cancers

• There are few established risk factors
  • High levels of ionizing radiation
  • Genetic syndromes

• Is having a structural birth defect a risk factor for childhood cancer?
Is having a structural birth defect a risk factor for childhood cancer?

• **Chromosomal abnormalities**
  - 6% of all birth defects
  - Trisomy 21

• **Single gene defects**
  - 7.5% of all birth defects
  - Neurofibromatosis type I

• **Multifactorial disorders (non-syndromic)**
  - 85% of all birth defects
  - Congenital heart disease

  ➔ Acute leukemia

  ➔ Optic glioma

  ➔ ???
Evaluating the association between childhood cancers and birth defects
Conclusions:

• Children with a birth defect had a 3-fold increased risk of developing cancer

• “Untangling the strong relation between birth defects and childhood cancers could lead to a better understanding of the genetic and environmental factors that affect both conditions.”
Are Children With Birth Defects at Higher Risk of Childhood Cancers?
Susan E. Carozza*, Peter H. Langlois, Eric A. Miller, and Mark Canfield

Risk of Cancer among Children with Birth Defects, Texas 1996-2005

<table>
<thead>
<tr>
<th>Birth Defect Group</th>
<th>IRR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal¹</td>
<td>15.52</td>
<td>11.66-20.27</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3.61</td>
<td>2.10-5.79</td>
</tr>
<tr>
<td>Neural tube</td>
<td>3.03</td>
<td>0.83-7.78</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3.50</td>
<td>2.81-4.31</td>
</tr>
<tr>
<td>Conotruncal</td>
<td>3.14</td>
<td>1.26-6.47</td>
</tr>
<tr>
<td>Oral clefts</td>
<td>2.69</td>
<td>1.34-4.82</td>
</tr>
<tr>
<td>Eye and ear</td>
<td>3.47</td>
<td>1.27-7.56</td>
</tr>
<tr>
<td>Anophthalmia/microphthalmia</td>
<td>6.91</td>
<td>2.24-16.14</td>
</tr>
<tr>
<td>Respiratory</td>
<td>3.58</td>
<td>1.16-8.36</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2.37</td>
<td>1.64-3.32</td>
</tr>
</tbody>
</table>

IRR=incidence rate ratio, CI=confidence interval, ¹ Includes trisomy 21, trisomy 13, and trisomy 18

*Measure giving an indication of the "strength of association, or how strongly two independent observations (BD vs. CC) are associated with each other. Higher IRR values signify an increased association between the two independent observations, suggesting that one (having BD) increases the risk for the other (developing CC)
Studies to Date...

• What is the risk of developing any childhood cancer if born with any birth defect
  • Comparison groups: *Grouped BD-Grouped CC*

• Risk of specific cancer if born with any birth defect
  • *Grouped BD-Specific CC*

• Risk of any cancer if born with specific birth defects
  • *Specific BD-Grouped CC*
## Linkage Studies: A Sample

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Period</th>
<th>Sample Size</th>
<th>Reported Associations</th>
<th>Molecular Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narod</td>
<td>1971-1986</td>
<td>20,304</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Altman</td>
<td>1984-1993</td>
<td>2,850</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Agha</td>
<td>1979-1996</td>
<td>90,400</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Rankin</td>
<td>1985-2001</td>
<td>599,290</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Bjørge</td>
<td>1967-2004</td>
<td>5.2 million</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Fisher</td>
<td>1988-2004</td>
<td>3.2 million</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Carozza</td>
<td>1996-2005</td>
<td>3.2 million</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Botto</td>
<td>1983-2006</td>
<td>2.8 million</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Dawson</td>
<td>1982-2007</td>
<td>641,036</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Janitz</td>
<td>1997-2009</td>
<td>591,235</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>
Unanswered Questions

• Are there specific birth defects that are associated with specific cancers?
  • While overall *having a birth defect is one of the strongest known risk factors for childhood cancer*, few studies have evaluated specific combinations

• Are there common mechanisms that may lead to the development of both outcomes?
  • Few large-scale efforts to conduct DNA sequencing among children with birth defects and childhood cancer
  • No Data Resources, combining both childhood cancer and birth defects genetic and clinical data, to help researchers study these conditions together
What is preventing these questions from being answered?

• **Identifying novel birth defect-childhood cancer (BD-CC) patterns among less common phenotypes AND describing the mechanisms underlying these patterns is challenging**

• **What is needed:**
  • Large population-based cohorts with sufficient numbers of childhood cancer and birth defects patients to allow meaningful estimation of specific cancer risk for specific birth defects
  • Biological samples for DNA sequencing
An example of identifying a specific BD-CC association:

birth defects & rhabdomyosarcoma*

* rare malignant tumor involving skeletal muscle tissue
Birth Defects and Rhabdomyosarcoma

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. (1995)</td>
<td>2.4 (0.9-6.5)</td>
</tr>
<tr>
<td>Altmann et al. (1998)</td>
<td>7.9 (2.2-28.8)</td>
</tr>
<tr>
<td>Agha et al. (2005)</td>
<td>1.9 (1.0-3.5)</td>
</tr>
<tr>
<td>Rankin et al. (2008)</td>
<td>3.0 (0.8-11.5)</td>
</tr>
<tr>
<td>Carozza et al. (2012)</td>
<td>2.1 (1.1-3.8)</td>
</tr>
<tr>
<td>Fisher et al. (2012)</td>
<td>2.3 (1.0-5.1)</td>
</tr>
<tr>
<td>Botto et al. (2013)</td>
<td>3.3 (0.9-12.3)</td>
</tr>
<tr>
<td>Michigan data</td>
<td>2.3 (1.5-3.5)</td>
</tr>
</tbody>
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RR = Relative Risk; Measure giving an indication of the "strength of association, or how strongly two independent observations (BD vs. CC) are associated with each other. Higher RR values signify an increased association between the two independent observations, suggesting that one (having BD) increases the risk for the other (developing Rhabdomyosarcoma).

Cancer Prevention Research Institute of Texas; award ID: RP140258; PI: Lupo
Birth Defects and Rhabdomyosarcoma: Meta-Analysis

Having a BD raises the odds of developing CC

OR = Odds Ratio; Measure giving an indication of the "strength of association. Quantifies how strongly the presence or absence of property A (birth defect) is associated with the presence or absence of property B (cancer) in a given population. OR>1 means that having "A" (birth defect) is considered to be "associated" with having "B" (cancer).

Cancer Prevention Research Institute of Texas; award ID: RP140258; PI: Lupo
# Birth Defects: COG* data

<table>
<thead>
<tr>
<th>Rhabdomyosarcoma (RMS) histology</th>
<th>RMS site</th>
<th>Birth defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonal</td>
<td>Leg</td>
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</tr>
<tr>
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<tr>
<td>Embryonal</td>
<td>Uterus</td>
<td>Genital defect</td>
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<tr>
<td>Embryonal</td>
<td>Prostate</td>
<td>Genital defect</td>
</tr>
<tr>
<td>Embryonal</td>
<td>Testis</td>
<td>Clubfoot</td>
</tr>
<tr>
<td>Embryonal</td>
<td>Testis</td>
<td>Cleft palate</td>
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<tr>
<td>Alveolar</td>
<td>Nasal cavity</td>
<td>Cleft palate</td>
</tr>
<tr>
<td>Embryonal</td>
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<td>Tracheoesophageal fistula</td>
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<tr>
<td>Embryonal</td>
<td>Ear</td>
<td>Genital defect</td>
</tr>
<tr>
<td>Embryonal</td>
<td>Unknown</td>
<td>Genital defect</td>
</tr>
<tr>
<td>Alveolar</td>
<td>Arm</td>
<td>Hip dysplasia</td>
</tr>
</tbody>
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6% of RMS cases also had a BD

*COG=Children’s Oncology Group; Cancer Prevention Research Institute of Texas; PI: Lupo
## Birth Defects: COG* data

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40% of the cases with RMS & a BD were in the same site

*COG=Children’s Oncology Group; Cancer Prevention Research Institute of Texas; PI: Lupo
A **risk factor** for childhood cancer is being born with a birth defect, suggesting that there are **shared genetic pathways** underlying some types of childhood cancer and structural birth defects.
Summary: studying childhood cancer and structural birth defects together

A risk factor for childhood cancer is being born with a birth defect, suggesting that there are shared genetic pathways underlying some types of childhood cancer and structural birth defects.
Summary: studying childhood cancer and structural birth defects together

A risk factor for childhood cancer is being born with a birth defect, suggesting that there are shared genetic pathways underlying some types of childhood cancer and structural birth defects.

These pathways may be unknown to researchers because there have been few large-scale genetics studies focusing on both childhood cancer and structural birth defects.
Summary: studying childhood cancer and structural birth defects together

Analyzing genetic sequence data from children with cancer and/or birth defects together may lead to the discovery of new genetic pathways that would not have been uncovered had the analysis only been performed using data from just one of the conditions.

- Children with specific birth defects could be candidates for prevention and screening clinics
- Cancer susceptibility and future therapeutic interventions

This is a unique aspect of the Kids First program.
Kids First Major Initiatives

1. Cohort identification and DNA sequencing
   • Covered in detail today during this webinar

2. Gabriella Miller Kids First Pediatric Data Resource
   • Covered in detail during a webinar tentatively planned for March/April 2017

3. Data Analysis
   • Covered in detail during a webinar tentatively planned for March/April 2017
Kids First Major Initiatives

1. Cohort identification and DNA sequencing
   • Identify children with childhood cancer and/or structural birth defects, and their families, for whole genome sequencing

2. Gabriella Miller Kids First Pediatric Data Resource

3. Data Analysis
Cohort identification and DNA sequencing

- **Cohort**: a group of people who share a common characteristic (childhood cancer or structural birth defects)

- **Pediatric research cohort**: a group of pediatric patients with a common characteristic, disease, or condition who have been recruited for a research study
How do researchers “find” the DNA changes causing or contributing to disease/conditions?

- **Step 1:** recruit cohorts and sequence their DNA

- **Step 2:** compare the DNA sequences of many children with cancer and/or birth defect to that of many parents with or without those conditions

```plaintext
ATC GGT ACT GAA ATG
TAG CCA TGA CTT TAC

Affected children

ATC GGT AAT GAA ATG
TAG CCA TTA CTT TAC

Affected or unaffected parents
```
How do researchers “find” the DNA changes causing or contributing to disease/conditions?

• **Step 2:** compare DNA sequences of children and parents

  • DNA changes that are shared between affected children that are **NOT** shared between unaffected parents could be causing/contributing to the cancer or structural birth defect

\[
\text{Affected children: } \text{ATC GGT A} \text{ACT GAA ATG} \\
\text{TAG CCA TAGA CTT TAC}
\]

\[
\text{Affected or unaffected parents: } \text{ATC GGT A} \text{AT GAA ATG} \\
\text{TAG CCA TT A CTT TAC}
\]
Selection of Cohorts for DNA Sequencing in 2015

- Rare cancers of the bone or soft tissue
- Bone tumors that were resistant to drug treatment
- Cleft lip and cleft palate
- Developmental disorders of facial nerves, such as those controlling eye movement
- Congenital Heart Defects
- Developmental disorders of the chest muscle used for breathing
- Disorders of Sex Development
Selection of Cohorts for DNA Sequencing in 2016

- Cancers of the nerves that help control involuntary function
- Cancer of the bone marrow that makes blood cells
- Diverse collection of Central Nervous System (CNS) and non-CNS solid tumors
- Congenital Heart Defects
- Developmental disorders of the chest muscle used for breathing
- Cleft lip and cleft palate
- Congenital hearing loss
- Abnormal curvature of the spine
1. Cohort identification and DNA sequencing

2. Gabriella Miller Kids First Pediatric Data Resource
   • Will greatly aid researchers in identifying DNA changes that cause or contribute to childhood cancer and/or structural birth defects

3. Data Analysis
Components of the Kids First Data Resource

Data Coordinating Center
- Facilitate deposition of sequence and phenotype data into relevant repositories
- Harmonize phenotypes

Data Resource Portal
- Web-based, public facing platform
- House, organize, index, and display data and analytic tools

Administrative and Outreach Core
- Develop policies and procedures
- Facilitate meetings and communication
- Educate and seek feedback from users
Kids First Major Initiatives

1. Cohort identification and DNA sequencing
2. Gabriella Miller Kids First Pediatric Data Resource

3. Data Analysis
   - 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
   - Support the development of new computational tools for analyzing large and complex genetics data sets
Data Analysis

• Provide funding to analyze data within the Kids First Data Resource
  • Both data generated by Kids First funds and data from other places that are integrated into the Kids First Data Resource

• Six NIH ICs* are providing additional funds to analyze childhood cancer and/or birth defects data
  • Researchers who receive funding agree to deposit their data into the Kids First Data Resource (if it’s not already there)

* NICHD, NCI, NIAAA, NIDCR, NINDS, NHLBI
Thank You! We Would Like to Know

• How do you anticipate that your organization would benefit from this program?
• What would success look like for this program? What are some short-term (3 year, 5 year, 10 year) metrics to measure success?
• If we are able to include additional activities in future years, what types of studies do you think would be most helpful?
• What sorts of information would you like to know as the data resource is being developed and about its use once it is established?
• How best can NIH keep the advocacy community apprised of the progress and activities of the Kids First program?
• What types of information will help strengthen the case for continued support of Kids First?

Submit Questions and Comments to the Kids First Mailbox kidsfirst@od.nih.gov