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
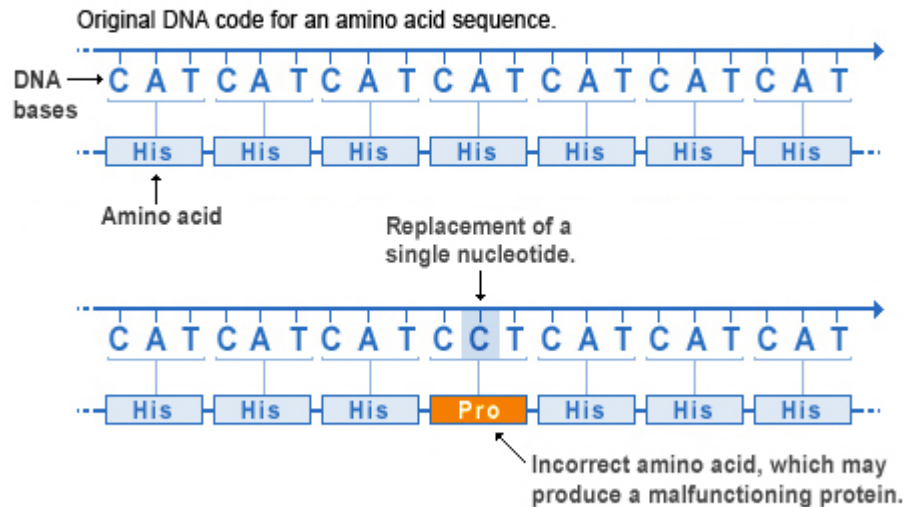
Genetic variation contributes to individual differences

- 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

Original DNA code for an amino acid sequence.

DNA bases → C A T C A T C A T C A T C A T C A T C A T

His | His | His | His | His | His | His

Amino acid

Replacement of a single nucleotide.

C A T C A T C A T C C T C A T C A T C A T

His | His | His | Pro | His | His | His

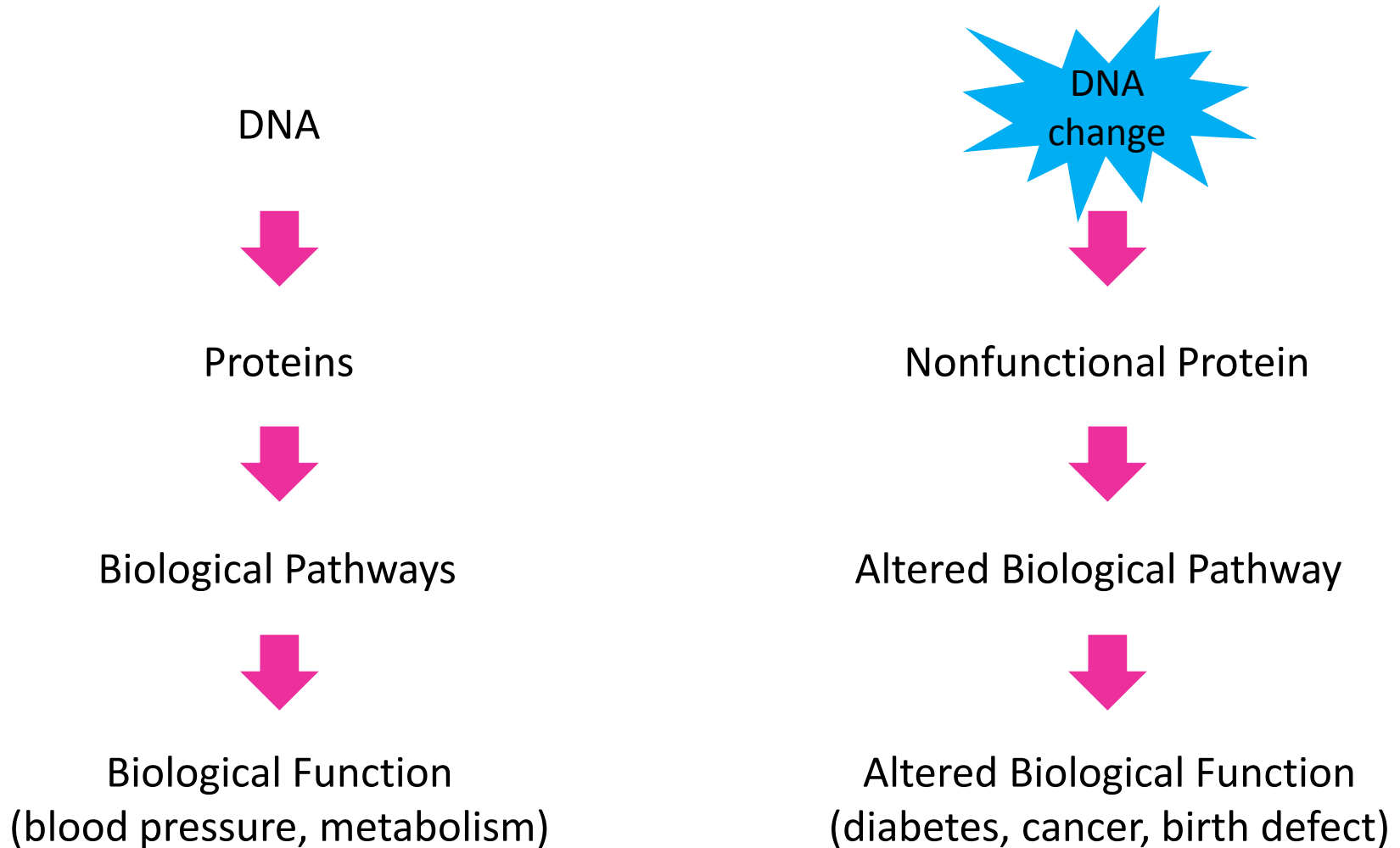Incorrect amino acid, which may produce a malfunctioning protein.

U.S. National Library of Medicine

- 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
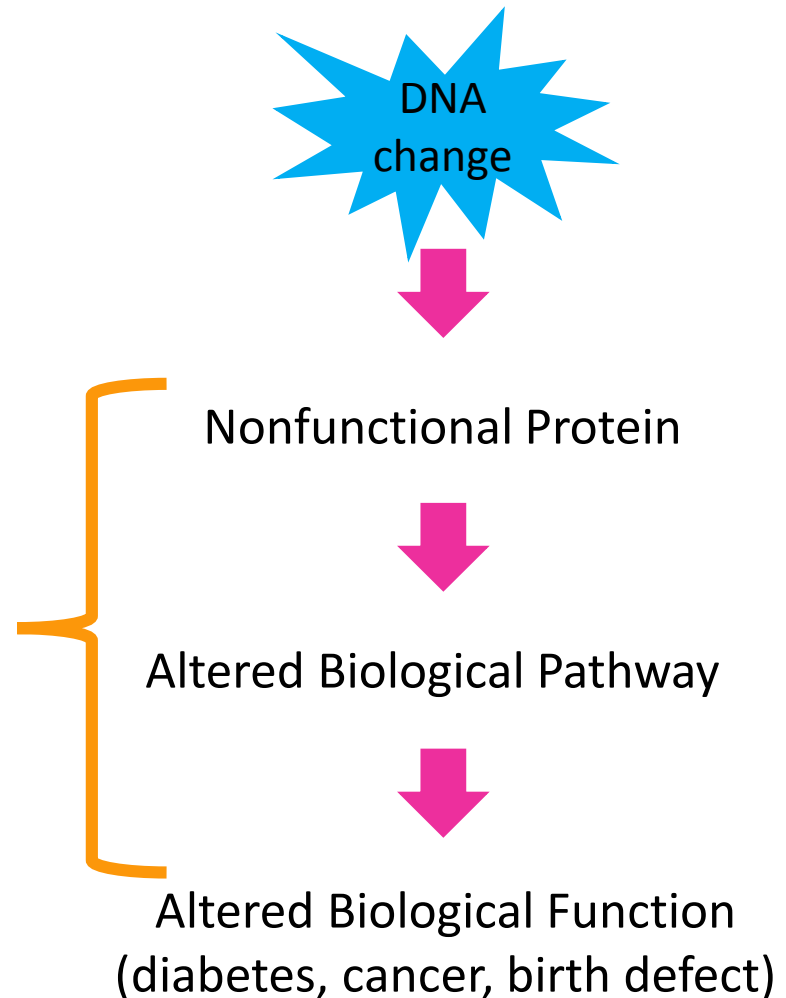
How will studying genetics help lead to treatments and cures?

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

DNA change

Nonfunctional Protein

Altered Biological Pathway

Altered Biological Function
(diabetes, cancer, birth defect)

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"

1 in every 33 babies is born with a birth defect.
We want to help you reduce that risk.
Learn more about prevention, detection, treatment and living with birth defects at www.cdc.gov/birthdefects.

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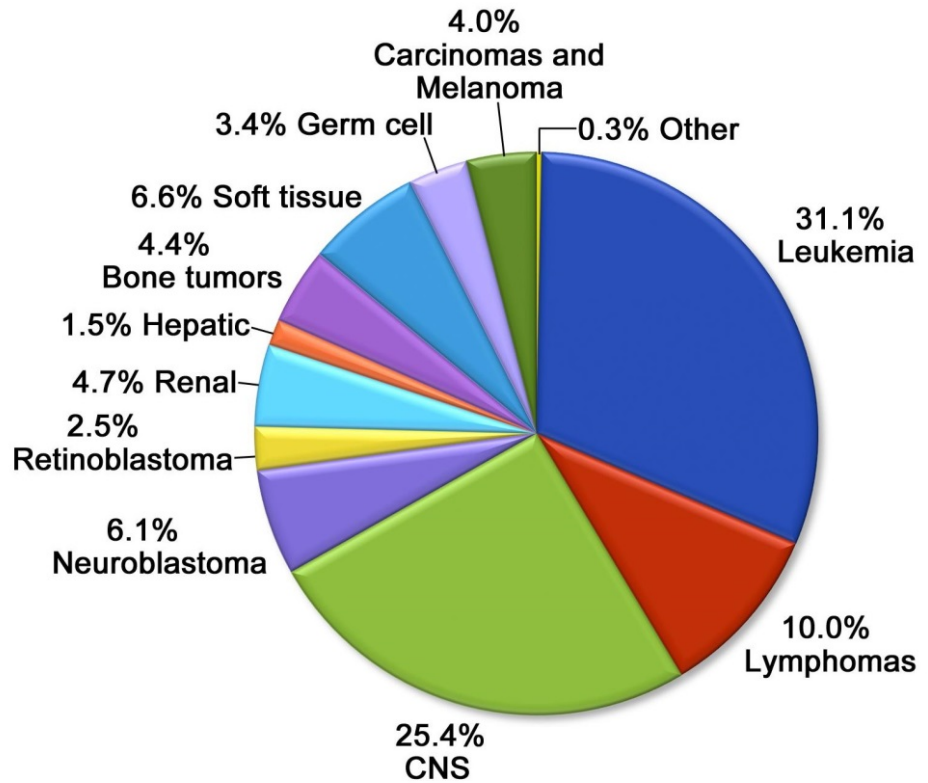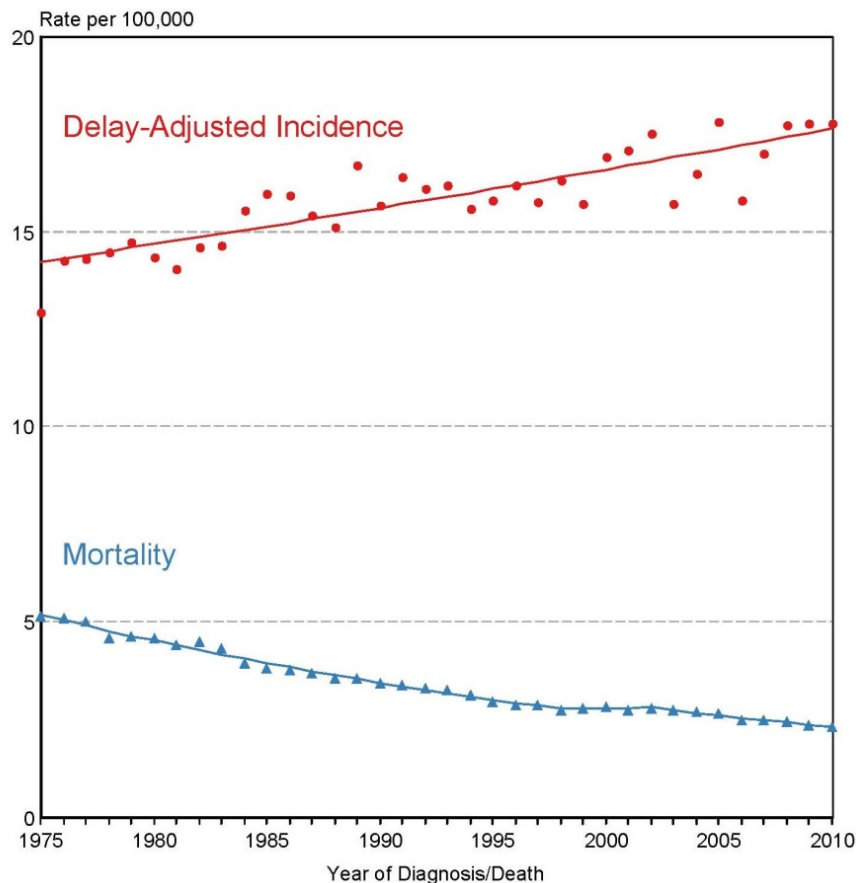
- **Multifactorial disorders (non-syndromic)**
  - 85% of all birth defects
  - Ex. Congenital heart disease

Childhood Cancers

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

Pie chart categories:
- 31.1% Leukemia
- 25.4% CNS
- 10.0% Lymphomas
- 6.6% Soft tissue
- 6.1% Neuroblastoma
- 4.7% Renal
- 4.4% Bone tumors
- 4.0% Carcinomas and Melanoma
- 3.4% Germ cell
- 2.5% Retinoblastoma
- 1.5% Hepatic
- 0.3% Other

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   ⟶ Acute leukemia

- **Single gene defects**
  - 7.5% of all birth defects
  - Neurofibromatosis type I   ⟶ Optic glioma

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

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Evaluating the association between childhood cancers and birth defects

Original Contribution

Are Children With Birth Defects at Higher Risk of Childhood Cancers?

Susan E. Carozza*, Peter H. Langlois, Eric A. Miller, and Mark Canfield

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

Birth Defect Group	IRR*	95% CI
Chromosomal[1]	15.52	11.66-20.27
Central nervous system	3.61	2.10-5.79
Neural tube	3.03	0.83-7.78
Cardiac	3.50	2.81-4.31
Conotruncal	3.14	1.26-6.47
Oral clefts	2.69	1.34-4.82
Eye and ear	3.47	1.27-7.56
Anophthalmia/microphthalmia	6.91	2.24-16.14
Respiratory	3.58	1.16-8.36
Genitourinary	2.37	1.64-3.32

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

First Author	Study Period	Sample Size	Reported Associations Grouped BD &/or CC	Specific BD & CC	Molecular Study
Narod	1971-1986	20,304	X	✔	X
Altman	1984-1993	2,850	✔	X	X
Agha	1979-1996	90,400	✔	X	X
Rankin	1985-2001	599,290	✔	X	X
Bjørge	1967-2004	5.2 million	✔	X	X
Fisher	1988-2004	3.2 million	✔	X	X
Carozza	1996-2005	3.2 million	✔	X	X
Botto	1983-2006	2.8 million	✔	X	X
Dawson	1982-2007	641,036	✔	X	X
Janitz	1997-2009	591,235	✔	X	X

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

Study	RR (95% CI)
Yang et al. (1995)	2.4 (0.9-6.5)
Altmann et al. (1998)	7.9 (2.2-28.8)
Agha et al. (2005)	1.9 (1.0-3.5)
Rankin et al. (2008)	3.0 (0.8-11.5)
Carozza et al. (2012)	2.1 (1.1-3.8)
Fisher et al. (2012)	2.3 (1.0-5.1)
Botto et al. (2013)	3.3 (0.9-12.3)
Michigan data	2.3 (1.5-3.5)

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)

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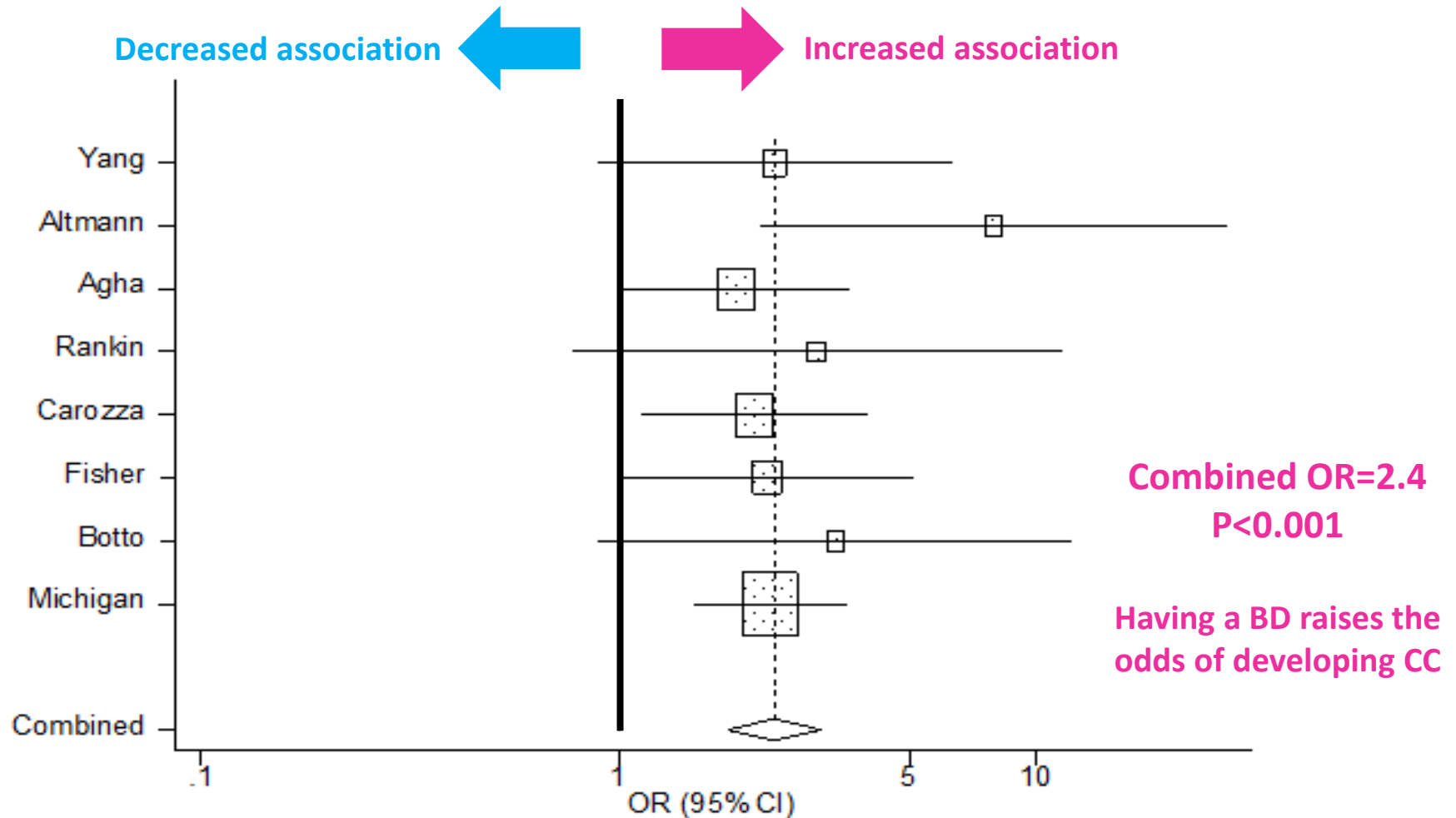
OR = Odds Ratio; Measure giving an indication of the "strength of association. Quantifies how strongly the presence or absence of property A (birth defect) is associated with the presence or absence of property B (cancer) in a given population. OR>1 means that having "A" (birth defect) is considered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

Birth Defects: COG* data

Rhabdomyosarcoma (RMS) histology	RMS site	Birth defect
Embryonal	Leg	Limb defect
Alveolar	Foot	Clubfoot
Alveolar	Arm	Clubfoot
Embryonal	Arm	Clubfoot
Embryonal	Uterus	Genital defect
Embryonal	Prostate	Genital defect
Embryonal	Testis	Clubfoot
Embryonal	Testis	Cleft palate
Alveolar	Nasal cavity	Cleft palate
Embryonal	Nasopharynx	Tracheoesophageal fistula
Alveolar	Nasopharynx	Clubfoot
Embryonal	Parameningeal	Gastrointestinal defect
Embryonal	Ear	Genital defect
Embryonal	Unknown	Genital defect
Alveolar	Arm	Hip dysplasia

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

Rhabdomyosarcoma (RMS) histology	RMS site	Birth defect
Embryonal	**Leg**	**Limb defect**
Alveolar	**Foot**	**Clubfoot**
Alveolar	Arm	Clubfoot
Embryonal	Arm	Clubfoot
Embryonal	**Uterus**	**Genital defect**
Embryonal	**Prostate**	**Genital defect**
Embryonal	Testis	Clubfoot
Embryonal	Testis	Cleft palate
Alveolar	**Nasal cavity**	**Cleft palate**
Embryonal	**Nasopharynx**	**Tracheoesophageal fistula**
Alveolar	Nasopharynx	Clubfoot
Embryonal	Parameningeal	Gastrointestinal defect
Embryonal	Ear	Genital defect
Embryonal	Unknown	Genital defect
Alveolar	Arm	Hip dysplasia

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

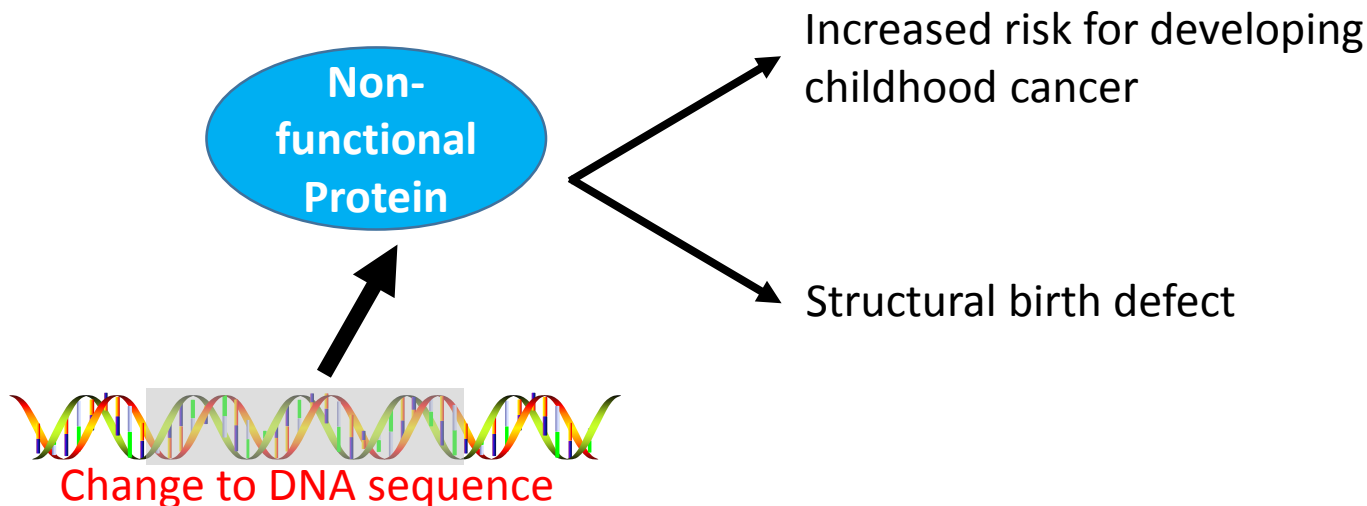*COG=Children's Oncology Group; Cancer Prevention Research Institute of Texas; PI: Lupo

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.

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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.

Non-functional Protein

Increased risk for developing childhood cancer

Structural birth defect

Change to DNA sequence

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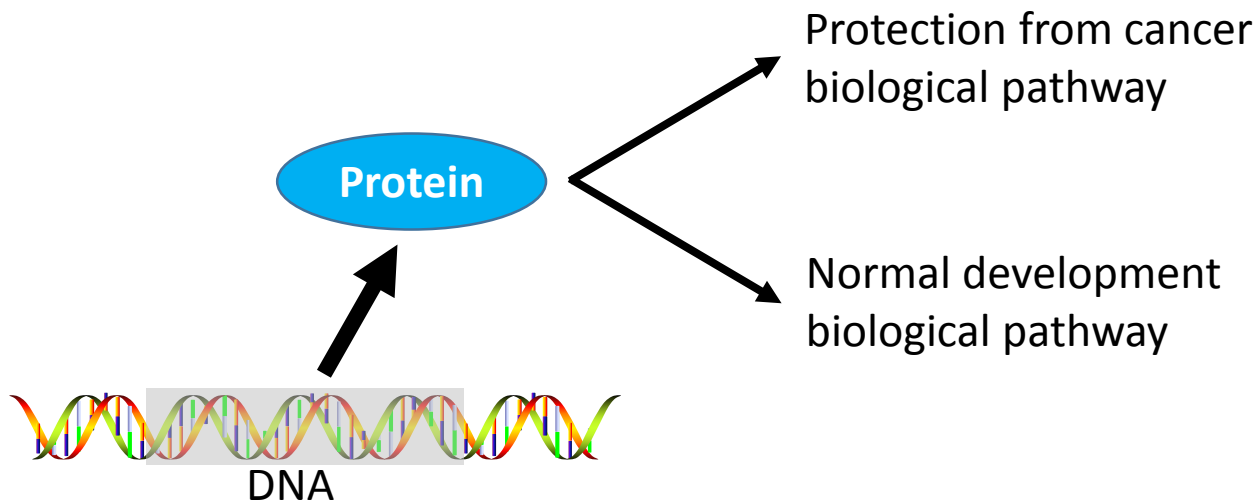
These pathways may be unknown to researchers because there have been few large-scale genetics studies focusing on both childhood cancer and structural birth defects

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

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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

ATC GGT AAT GAA ATG
TAG CCA TTA CTT TAC

Affected children

ATC GGT ACT GAA ATG
TAG CCA TGA 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

ATC GGT A**C**T GAA ATG
TAG CCA T**G**A CTT TAC

Affected or unaffected parents

ATC GGT A**A**T GAA ATG
TAG CCA T**T**A CTT TAC

Affected children

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

Kids First Major Initiatives

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