Meeting of the Interagency Autism Coordinating Committee

Tuesday, October 24, 2017

National Institutes of Health
6001 Executive Boulevard (Neuroscience)
Conference Room C & D
Rockville, MD 20852

Conference Call Access:
Phone: 800-369-1740
Access Code: 5135863

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Meeting of the IACC

Morning Agenda

9:00 AM **Welcome, Introductions, Roll Call and Approval of Minutes**

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

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Meeting of the IACC

Morning Agenda – continued

9:10 **The HHS Report to Congress on Young Adults and Transitioning Youth with Autism Spectrum Disorder**

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

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Meeting of the IACC

Morning Agenda – continued

9:30 **Update on CDC Study to Explore Early Development (SEED)**

Autism Activities at CDC
Nicole Dowling, Ph.D.
Chief, Development Disabilities Branch, CDC

SEED: Overview of Methods and Data Collection
Laura Schieve, Ph.D.
Epidemiologist, Developmental Disabilities Branch, CDC

Highlights of the Findings of 5 SEED Studies

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Meeting of the IACC

Morning Agenda – continued

ASD Risk Factors Study: Maternal Infection and Fever during Pregnancy and Risk of Autism Spectrum Disorder

Presented by **M. Daniele Fallin, Ph.D.**
Sylvia and Harold Halpert Professor and Chair, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Joint Appointment in Medicine on behalf of **Lisa Croen, Ph.D.** Senior Research Scientist, Kaiser Permanente

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Meeting of the IACC

Morning Agenda – continued

ASD Genetic Associations: Peripheral Blood DNA Methylation and ASD
M. Daniele Fallin, Ph.D.
Sylvia and Harold Halpert Professor and Chair, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Joint Appointment in Medicine

ASD and Child Health Effects: Gastrointestinal Symptoms in 2 – 5 Year Old Children
Ann Reynolds, M.D.
Associate Professor, Pediatrics – Developmental Pediatrics
University of Colorado School of Medicine

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Meeting of the IACC

Morning Agenda – continued

ASD and Child Health Effects: Gastrointestinal Symptoms in 2 – 5 Year Old Children

Ann Reynolds, M.D.
Associate Professor, Pediatrics – Developmental Pediatrics
University of Colorado School of Medicine

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Meeting of the IACC

Morning Agenda – continued

Characteristics of Children with ASD: A Novel Protocol for Characterizing Dysmorphology to Enhance the Phenotypic Classification of ASD
Stuart Shapira, M.D., Ph.D.
Chief Medical Officer and Associate Director for Science National Center Birth Defects and Developmental Disabilities
CDC

10:45 **Morning Break**

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Meeting of the IACC

Morning Agenda – continued

11:00 **Committee Business**

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

12:00 **Lunch**

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HHS Report to Congress: Young Adults and Transitioning Youth with Autism Spectrum Disorder

Susan Daniels, Ph.D.
Director, Office of Autism Research Coordination
Executive Secretary, IACC
National Institute of Mental Health

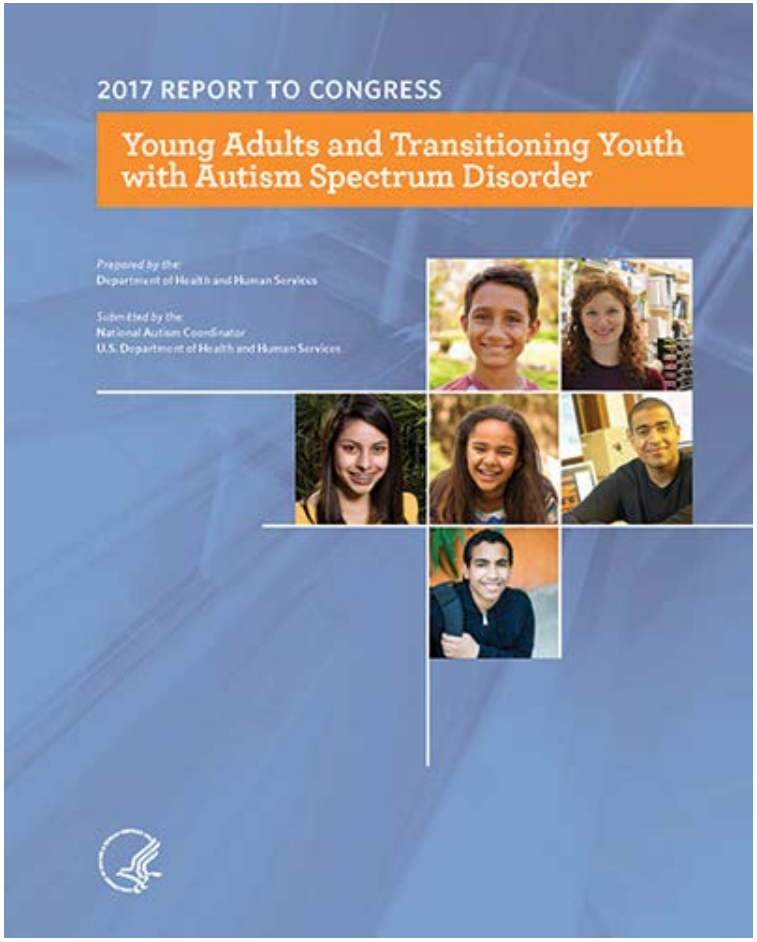
Autism CARES Act Supports Federal Autism Activities

- Autism CARES Act signed into law on August 8, 2014
  - CARES = Collaboration, Accountability, Research, Education, and Support
  - Reauthorization of federal laws previously known as Combating Autism Act of 2006 and CARA of 2011
- Reauthorization of Interagency Autism Coordinating Committee (IACC)
- Requirement for a Report to Congress on Young Adults and Youth Transitioning to Adulthood on the autism spectrum
- Requirement for a report to Congress on all federal activities related to ASD
- Reauthorized support for autism-focused efforts from FY15-19

Report to Congress Mandated by Autism CARES Act of 2014 (P.L. 113-157)

Purpose

- Summarize existing Federal investments in transition research and services activities
- Identify gaps in Federal research, programs, and services that support youth with ASD during the transition to adulthood



Process for Developing the Report

- The office of the HHS National Autism Coordinator convened a federal working group to develop the report
- The Steering Group for the report:
  - **Thomas E. Novotny**, M.D., M.P.H., HHS National Autism Coordinator
  - **Susan Daniels**, PhD, Director, Office of Autism Research Coordination National Institutes of Health
  - **Alicia Richmond Scott**, M.S.W., Office of the Assistant Secretary for Health
  - **Robin Harwood**, Ph.D. Health Scientist, Office of the Assistant Secretary for Health Office of the Secretary and Health Resources and Services Administration
  - **Julianna Rava**, M.P.H. Science Policy Analyst, Office of Autism Research Coordination National Institutes of Health U.S. Department of Health and Human Services
- Stakeholder Expert Panel and IACC Stakeholder Input
  - To provide input on gaps and opportunities

Interdepartmental Transition Workgroup

- U.S. Dept. of Health and Human Services: 15 agencies and HHS offices represented on the workgroup –
- NIH, HRSA, CDC, CMS, FDA, AHRQ, ACL, ACF, IHS, SAMHSA, HHS offices: OASP, ASPE, ASL, OGA, OASA
- U.S. Dept. of Labor
- U.S. Dept. of Education
- U.S. Dept. of Transportation
- U.S. Dept. of Housing and Urban Development
- U.S. Dept. of Justice
- U.S. Dept. of Defense
- U.S. Social Security Administration
- 34 members

Stakeholder Expert Panel

- **Kristy Anderson**, M.S.W., A.J. Drexel Autism Institute Drexel University
- **Scott Badesch** President, Autism Society
- **Julia Bascom**, Autistic Self Advocacy Network
- **Shelby Crants**, Autism Speaks
- **Marc Ellison**, Ed.D., Marshall University
- **Angela Lello**, Autism Speaks
- **David Mandell**, Sc.D. University of Pennsylvania
- **Margaret (Peggy) McManus**, MHS Got Transition
- **Anne Roux**, M.P.H., M.A., A.J. Drexel Autism Institute Drexel University
- **Paul Shattuck**, Ph.D., A.J. Drexel Autism Institute Drexel University
- **Stuart Spielman**, Esq., Autism Speaks
- **Julie Lounds Taylor**, Ph.D. Vanderbilt University
- **Patience White**, M.D., M.A., Got Transition

Structure of the Report

- Part 1: Background Information on ASD and the Transition to Adulthood
- Part 2: Overview of Relevant Federal Programs
- Part 3: Input from Key Stakeholders
- Part 4: Conclusions and Recommendations

Background - Overview

- Transition period challenges:
  - Complexities caused by the heterogeneity of ASD and any co-occurring health and mental health conditions – represents a wide variety of needs
  - Magnified by complexities in transitioning from a set of supports coordinated around and through the educational system to a set of health and social service systems geared to adults that may be provided by many different agencies and services that are not necessarily coordinated

Background Information
Scope of Need

- **Population Characteristics**
  - Estimated 50,000 youth with ASD turn 18 each year
    - Currently, about 450,000 youth with ASD aged 16-24 years old in U.S.
- **Health and Wellbeing: Secondary School**
  - When compared to all youth with IEPs, youth with ASD who have IEPs are:
    - More likely to have a co-occurring chronic health or mental health condition
    - Less likely to be able to manage independently and develop friendships
    - Less likely to take steps to prepare for college and employment

Background Information
Scope of Need

- **Health and Wellbeing: Young Adults (20-25 years old)**
  - Young adults with ASD who had IEPs in high school:
    - Less than 1 in 5 had ever lived independently following high school
    - Nearly two-thirds received Supplemental Security Income (SSI) benefits
    - Only 58% had ever worked during their early 20s
    - Only 36% of youth with ASD had ever participated in postsecondary education or training of any kind between high school and their early 20s

Background Information
Scope of Need

- **Health and Wellbeing: Adulthood**
  - Adults with ASD, compared to the general population:
    - Die an average of 16 years earlier than people not on the spectrum
    - Are 40 times more likely to die prematurely of a neurological condition (such as epilepsy) if they also have a learning disability
    - Are 9 times more likely to die from suicide
    - Are at heightened risk for co-occurring conditions such as depression and anxiety
    - Are at higher risk for other non-communicable diseases including diabetes and heart disease

Stakeholder Input from IACC

Topics that emerged through IACC Public Comment:

- Services and Supports Based on Individual Needs
- Postsecondary education and training;
- Employment opportunities
- Treatment for concurrent conditions, and access to occupational, speech, and language therapies
- Housing
- Transportation supports
- Community integration services and supports
- Coordinated, ‘wraparound’ services
- Relief from barriers to access, coordinate, and finance what are experienced as ‘piecemeal’ services on their own, or services they may not even be aware of
- Transition supports and information beginning in early adolescence

Stakeholder Input from Expert Panel

Gaps in Research

- Descriptive data
- Existing programs available to study
- Outcomes research
- Research on access and barriers to service

Gaps in Services and Programming

- Individualized planning
- Coordinated, comprehensive care responsive to individual needs
- Transition planning
- High-quality services and programming that challenge
- Better coordination of services
- Strengthened workforce
- Increased access

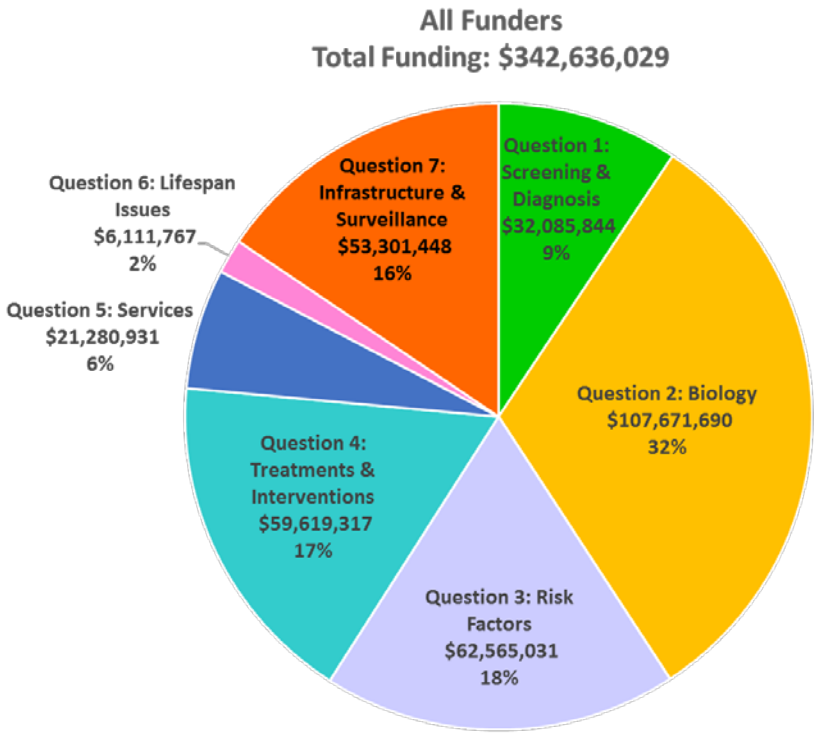
Background Information
Challenges and Barriers to Service

- Coordination of complex service and support needs across multiple systems
- Access to needed resources, which may be limited in availability
- Access to services and supports to facilitate managing a complex condition and co-occurring health conditions
- Achievement and management of independent living
- Development of meaningful relationships and broader social networks as the individual desires
- Lack of availability of and consistency in ASD-specific training
- Communication challenges faced by adults with ASD in accessing and interacting with health service providers
- Need to build greater community understanding and acceptance of neurodiversity that ASD represents

Overview of Relevant Federal Programs

Research

- NIH, HRSA, ED, and DOD funded18 projects devoted to transitioning youth with ASD funded between FY13 and FY16
- IACC Portfolio Analysis: Lifespan issues (including transition) received 2 percent ($6.1 million) of overall combined federal and private ASD funding in 2015



Overview of Relevant Federal Programs

Programs that Provide Services and Supports

- Mainstream Programs available to all U.S. citizens meeting eligibility requirements
  - Do not usually track ASD
- Cross-Disability Services and Supports
  - Most do not track utilized services and goals according to specific diagnoses such as ASD
  - Eligibility requirements vary
- Autism CARES Act Programs
  - Population surveillance and risk factor research at CDC
  - Capacity building through training and intervention research at HRSA

Overview of Relevant Federal Programs
Summary

- ASD-related research and programming conducted under and administered through multiple agencies
- Most provide broadly targeted programs that individuals with ASD may be eligible for if they meet program criteria
  - In most cases, these programs do not track specific diagnoses such as ASD due to cost and overall program goals to serve based on need rather than diagnosis
  - This presents a challenge in collecting data

Report Conclusions

A Need For:

- Coordinated, comprehensive approach to services and supports
- Support coordination across service systems
- Family and Caregiver Support
- Data and Research on Transition-age youth and Young Adults with ASD

Recommendations

Epidemiological Data Collection and Monitoring

- Assess and monitor experiences, needs, and life goals of transitioning youth with ASD
- National survey assessing full range of service and support needs, barriers, and facilitators
- More complete surveillance system to provide data on full spectrum of transition-age youth and young adults with ASD
- Longitudinal data to follow up on transition outcomes for individuals with ASD

Recommendations

Research needs:

- Targeted outcome research to assess efficacy of transition-oriented programs
- Program model development and testing
- Meaningful outcome measures
- Implementation and service delivery research
- Encouragement of more research specifically on transitioning youth and young adults with ASD and their caregivers

Recommendations

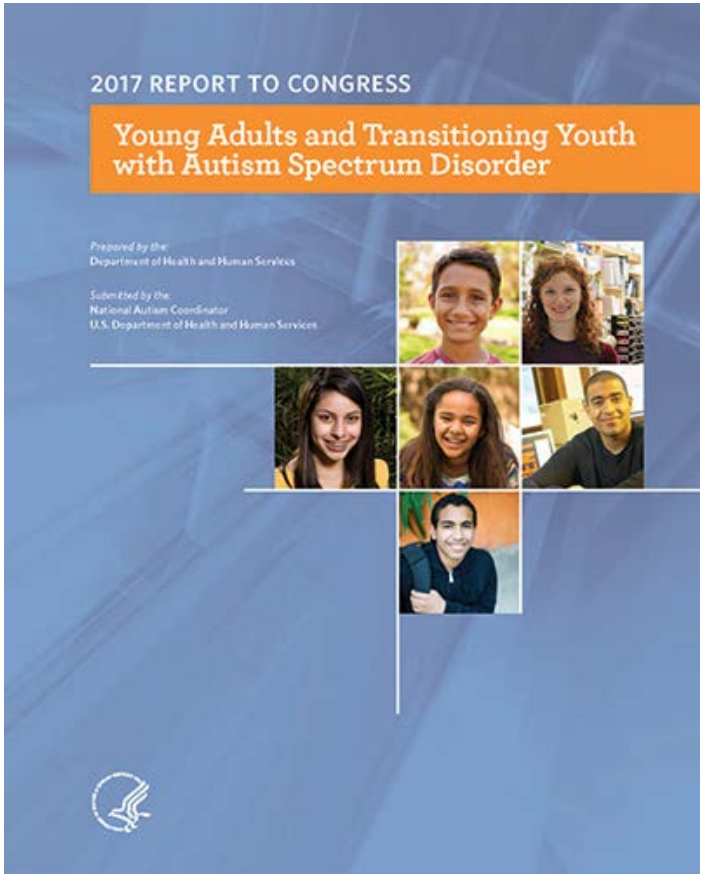
Program Services and Delivery

- Coordination is necessary across federal agencies, and across service systems at state and community levels
- Programs must be designed for broad access, but with individual flexibility
- Trained personnel are vital to help families navigate multiple, complex service systems
- Better preparation of all relevant adult service and support providers is essential
- Increased coordination is needed between youth and adult services and supports
- Federal policies that encourage blending and braiding of funds across agencies are critical
- Concerted communications efforts are crucial to dispel stigma and encourage acceptance

Follow Up

- The HHS Office of the National Autism Coordinator was leading efforts to follow up on this report
- Seeking opportunities to collaborate with the Federal Partners for Transition (FPT) working group
- FPT is a workgroup with representatives of several **federal** agencies, including the Departments of Education, Health and Human Services, and Labor, and the Social Security Administration, was formed in 2005 to support all youth, including youth with disabilities, in successfully.
- 2020 Federal Youth Transition Plan: A Federal Interagency Strategy
- Future opportunities to collaborate with IACC?

Report Available Online



https://iacc.hhs.gov/publications/report-to-congress/2017/

National Center on Birth Defects and Developmental Disabilities

Autism Activities at CDC: Update on The Study to Explore Early Development (SEED)

Nicole F. Dowling, PhD

Chief, Developmental Disabilities Branch
Division of Congenital and Developmental Disorders
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

Interagency Autism Coordinating Committee Meeting

October 24, 2017

The Study to Explore Early Development (SEED)

- **One of the largest studies** in the United States looking at ASD risk factors
  - Already enrolled over **6,000** children and their families
- Will **contribute to growing and complex body of knowledge** around what puts children at greater risk for ASD
  - Key strength of SEED = ability to simultaneously look at detailed information on characteristics of ASD, environmental factors, and genes and to assess interactions
- Inclusion of **bio-specimens**
  - Genetic assays completed for a portion of bio-specimens

National Center on Birth Defects and Developmental Disabilities

Division of Human Development and Disability

Division of Blood Disorders

Division of Congenital and Developmental Disorders

Division of Congenital and Developmental Disorders

- Vision

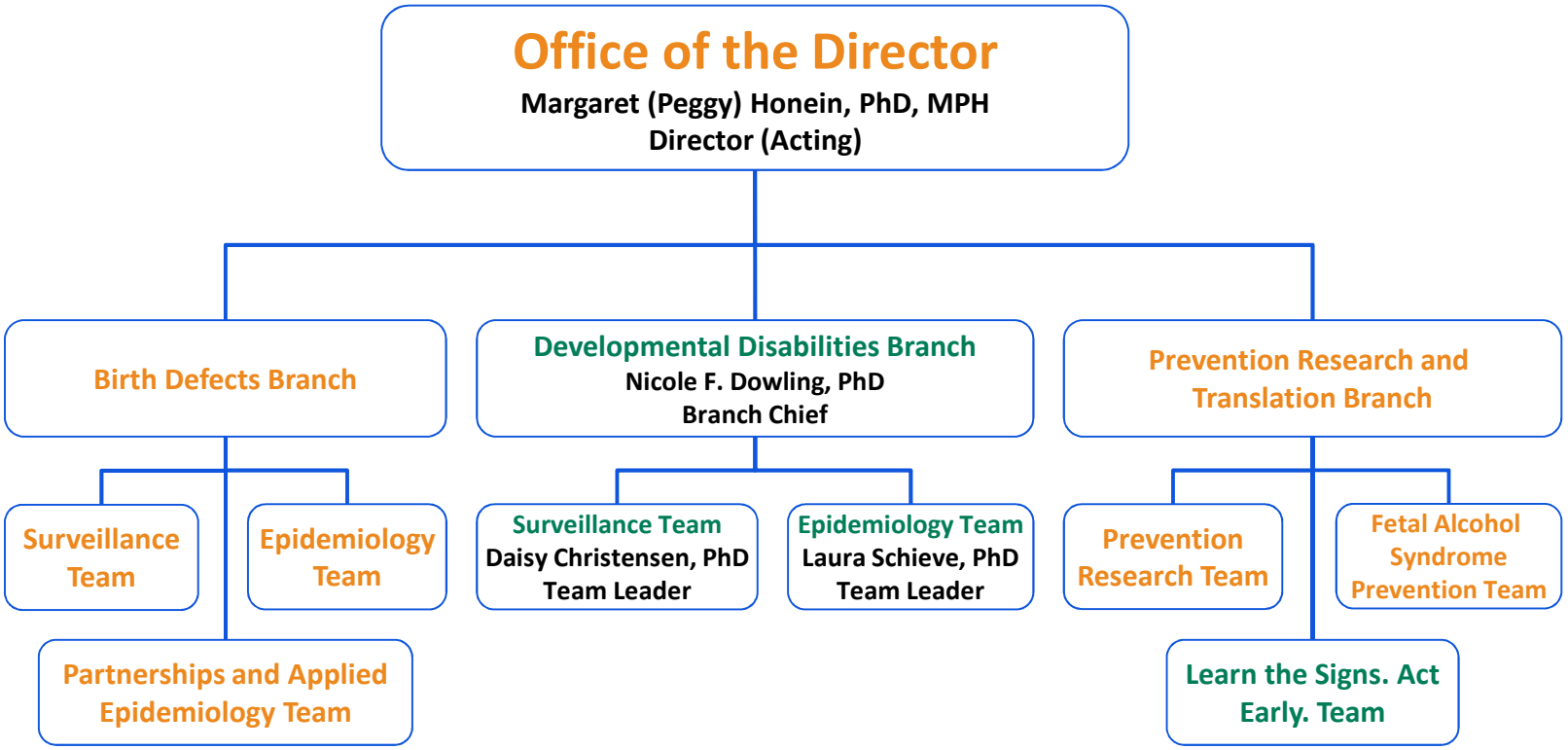
  Healthy birth and optimal development for all children

- Mission

  To be the public health leader in preventing the occurrence or adverse consequences of birth defects, developmental disabilities, and pediatric genetic conditions through surveillance, research, and intervention programs

- Role
  - Develop and support state-of-the-art surveillance programs
  - Conduct research into causes and risk factors
  - Develop, implement and evaluate prevention programs

Division of Congenital and Developmental Disorders



CDC's Autism Programs

Track

- **Autism and Developmental Disabilities Monitoring (ADDM) Network**
- Track the number and characteristics of children with Autism Spectrum Disorder (ASD) and other developmental disabilities.

Research

- **Study to Explore Early Development (SEED)**
- Research what puts children at greater risk for ASD.

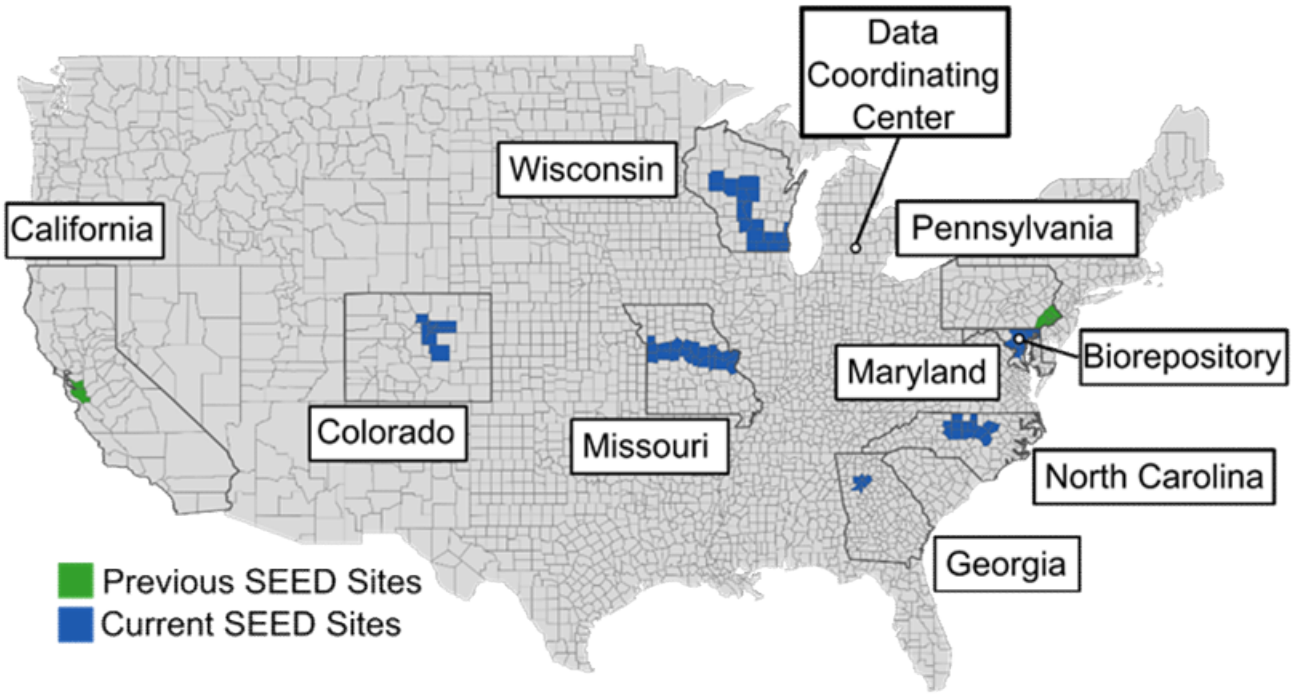
Act Early

- **Learn the Signs. Act Early.**
- Improve early identification of developmental delays and disabilities so children and families can get the help they need.

The Study to Explore Early Development (SEED)

- SEED case-control study
  - Fund and oversee research activities at 5 extramural sites
  - CDC participates as 6th intramural site
  - 3 phases funded to date
  - Fund central bio-repository (all phases)
  - Fund and oversee Data Coordinating Center (all phases)
- SEED Teen Follow-up Study (SEED Teen)
  - Fund and oversee research activities at 1 extramural site
  - CDC participates as 2nd intramural site
  - First phase funded in 2016
  - Data collection expected to begin early 2018

The Study to Explore Early Development (SEED)



Agenda for Today's Presentation

SEED: Overview of Methods and Data Collection – Laura Schieve, PhD

Highlights of the Findings of 5 SEED Studies

ASD Risk Factors Studies

- ***Autism Spectrum Disorder and Birth Spacing*** – Laura Schieve, PhD
- ***Maternal Infection and Fever during Pregnancy and Risk of Autism Spectrum Disorder*** – presented by M. Danielle Fallin, PhD on behalf of Lisa Croen, PhD

ASD Genetic Associations

- ***Peripheral Blood DNA Methylation and ASD*** – M. Danielle Fallin, PhD

ASD and Child Health Effects

- ***Gastrointestinal Symptoms in 2 – 5 Year Old Children*** – Ann Reynolds, MD

Characteristics of Children with ASD

- ***A Novel Protocol for Characterizing Dysmorphology to Enhance the Phenotypic Classification of ASD*** – Stuart Shapira, MD

The Study to Explore Early Development

Laura A. Schieve, PhD

Lead, Epidemiology Team, Developmental Disabilities Branch

National Center on Birth Defects and Developmental Disabilities

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SEED Research Objectives

- Assess etiologic risk factors for ASD
  - Focus on
    - Genetics
    - Non-genetic exposures in pregnancy
- Characterize ASD phenotypic subtypes
- Assess health of children with ASD and other developmental disabilities

SEED Methods

Case-control study – designed to enroll demographically diverse population of children from various U.S. areas

3 groups of children and their mothers are invited

- **ASD Group**

  identified from clinics and schools that conduct developmental exams on children residing in defined population area for each site

- **Comparison Group 1 – Other Developmental Delays (DD)**

  identified from same sources as ASD gp

- **Comparison Group 2 – Population Controls (POP)**

  sampled from birth records at each site

SEED Methods

- Birth cohorts:
  - *SEED 1: 2003-2006*
  - *SEED 2: 2008-2011*
  - *SEED 3: 2014-2017*

- Children 30-68 months of age during data collection

SEED Methods

Rigorous case classification methods

- At enrollment, children have presumptive classification – ASD, DD, POP
- **All** children screened for autism symptoms -- *Social Communication Questionnaire* (SCQ)
- Children with high SCQ score or a previous ASD diagnosis considered **possible ASD cases**
- Possible ASD cases undergo confirmatory assessments -- *ADOS and ADI-R (Autism Diagnostic Observation Schedule, Autism Diagnostic Interview-Revised)*
- Children meeting SEED study criteria on ADOS and ADI-R classified as cases

SEED Methods, Data Collection

Study Instrument	SEED 1
Social Communication Questionnaire	X
Maternal Telephone Interview *Family socio-demographics, maternal reproductive health & pregnancy exposures*	X
Self-administered Forms *Family and child health and child behaviors and development*	X *(12)*
In Person Child Developmental Assessment *All -- Mullen Scales of Early Learning* *Possible ASD cases –ADOS, ADI-R, Vineland Adaptive Behavioral Scales*	X
Buccal and Blood Samples *Collected from child, mother, and father if available*	X
Dysmorphology Exam	X
Diet and Stool Diaries	X
Medical Record Abstractions *Maternal prenatal care, labor & delivery, and child neonatal, pediatric records*	X

SEED Methods, Data Collection

Study Instrument	SEED 1	SEED 2
Social Communication Questionnaire	X	**X**
Maternal Telephone Interview *Family socio-demographics, maternal reproductive health & pregnancy exposures*	X	**X**
Self-administered Forms *Family and child health and child behaviors and development*	X *(12)*	**X** ***(6)***
Maternal and Child Residential History Form		**X**
In Person Child Developmental Assessment *All -- Mullen Scales of Early Learning* *Possible ASD cases –ADOS, ADI-R, Vineland Adaptive Behavioral Scales*	X	**X**
Saliva and Blood Samples *Collected from child, mother, and father if available*	X	**X**
~~Dysmorphology Exam~~	X	
Child Measurements *Weight, height, head circumference*		**X**
~~Diet and Stool Diaries~~	X	
Medical Record Abstractions *Maternal prenatal care, labor & delivery, and child neonatal, pediatric records*	X	**X**

SEED Methods, Data Collection

Study Instrument	SEED 1	SEED 2	SEED 3
Social Communication Questionnaire	X	X	**X**
Maternal Telephone Interview *Family socio-demographics, maternal reproductive health & pregnancy exposures*	X	X	**X**
Self-administered Forms *Family and child health and child behaviors and development*	X *(12)*	X *(6)*	**X** ***(6)***
Maternal and Child Residential History Form		X	**X**
In Person Child Developmental Assessment *All -- Mullen Scales of Early Learning* *Possible ASD cases –ADOS, ADI-R, Vineland Adaptive Behavioral Scales*	X	X	**X**
Saliva and Blood Samples *Collected from child, mother, and father if available*	X	X	**X**
~~Dysmorphology Exam~~	X		
Child Measurements *Weight, height, head circumference*		X	**X**
~~Diet and Stool Diaries~~	X		
~~Medical Record Abstractions~~ ~~*Maternal prenatal care, labor & delivery, and child neonatal, pediatric records*~~	X	X	

SEED Sample Summary

Final Study Classification	ASD	DD	POP	Total
SEED 1	707	1270	1223	3200
SEED 2	773	1060	1066	2899
Total	1480	2330	2289	6099

SEED Analyses

- **SEED 1** -- analyses ongoing
  - >40 papers completed (17 published or In Press)
  - >40 analyses in progress
- **SEED 2** – analytic files recently finalized, many new analyses with expanded sample size being planned
- **SEED 3** – data collection began in August

SEED Teen

SEED Teen Research Objectives

To assess and compare adolescents with ASD, with other DDs, and adolescents in the general population (POP)

- Developmental trajectory from preschool age to adolescence
- Health and functioning
- Healthcare utilization and needs
- Education attainment and needs
- Family impacts

SEED Teen Overview

- First phase is a follow-up of children enrolled in SEED 1 case-control study
- 4 sites included: *GA, MD, NC, PA*
- Data collection will occur when children ~14-15 years of age
- Sample size estimates of eligible children

ASD	DD	POP	Total
381	542	487	1410

SEED Teen Data Collection

Mother or other primary caregiver asked to complete

- 2 questionnaires
  - ***Social Responsiveness Scale*** – standardized instrument that was also included in the case-control study
  - ***SEED Teen Health and Development Survey*** -- developed by SEED Teen investigators
  - Total time to complete ~1 hour

- Supplemental consent form to share genetic data from biosamples obtained previously with NIH repositories

Highlights of SEED Analyses and Findings

ASD Risk Factors Studies

- ***Autism Spectrum Disorder and Birth Spacing***– *Laura Schieve, PhD*
- ***Maternal Infection and Fever during Pregnancy and Risk of Autism Spectrum Disorder*** – *presented by M. Danielle Fallin, PhD on behalf of Lisa Croen, PhD*

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- ***A Novel Protocol for Characterizing Dysmorphology to Enhance the Phenotypic Classification of ASD*** *-- Stuart Shapira, MD, PhD*

National Center on Birth Defects and Developmental Disabilities

Autism Spectrum Disorder and Birth Spacing: Findings from the Study to Explore Early Development

LA Schieve, LH Tian, C Drews-Botsch, GC Windham, C Newschaffer, JL Daniels, LC Lee, LA Croen, MD Fallin

Interagency Autism Coordinating Committee Meeting

October 24, 2017

Background and Study Objective

- Previous studies reported associations between ASD and birth spacing. But they had some limitations
  - Case definitions based on non-standardized diagnostic coding
  - Limited assessment of phenotypic case subtypes
  - No assessment of other (non-ASD) developmental disabilities
  - Little examination of possible underlying mechanisms for associations

- SEED was able to address these limitations
  - Rigorous case classification based on gold standard instruments
  - Extensive developmental data to characterize phenotypic subtypes
  - Second non-ASD DD case group enrolled
  - Detailed maternal health data allowed exploration of possible mechanisms

Methods

- Analysis sample: children who were 2nd or later births

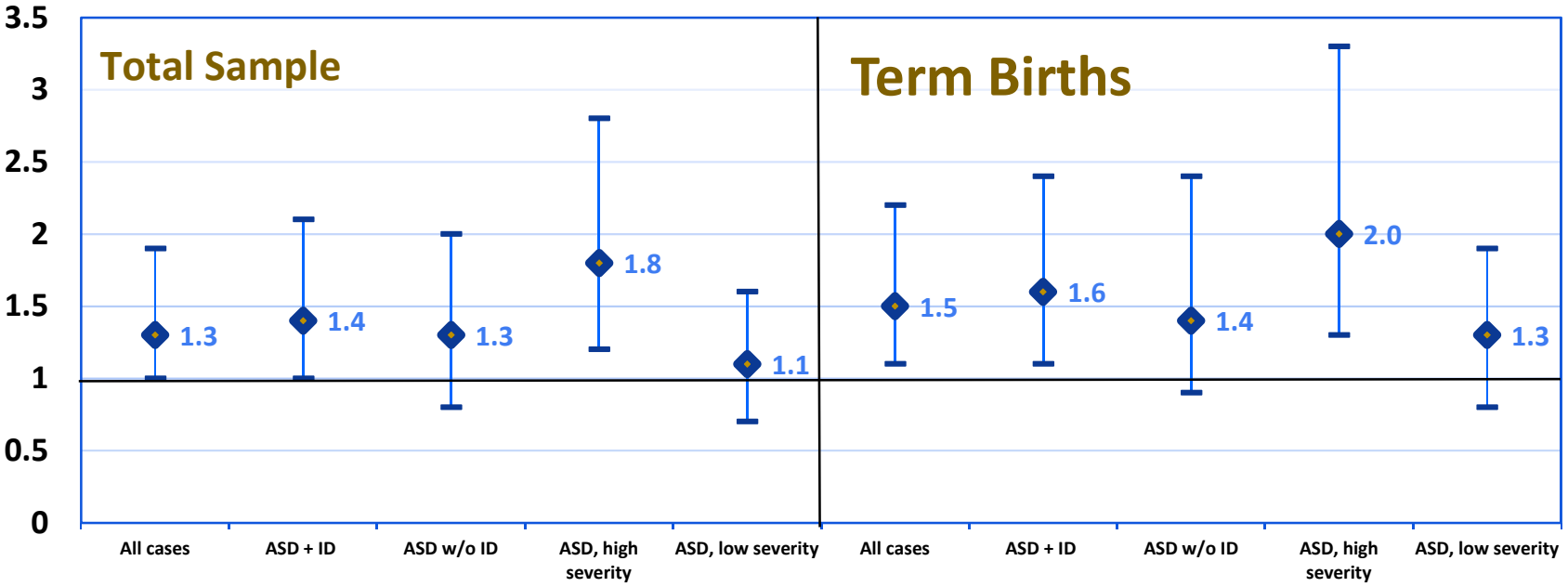
- Inter-pregnancy interval (IPI) -- time between mother's previous birth and conception of the study child's birth
  - Short birth spacing: IPI <18 months *(16% POP controls)*
  - Long birth spacing: IPI ≥60 months *(33% POP controls)*

- Case groups compared to POP controls
  - **ASD (total)**
  - ASD + intellectual disability (ID) vs ASD w/out ID
  - ASD with high symptom severity score vs ASD w/ lower symptom severity score *(measured on ADOS)*
  - **DD (total)**
  - DD + ID vs DD w/out ID
  - DD with ASD features vs DD without ASD features *(measured on SCQ)*

Methods

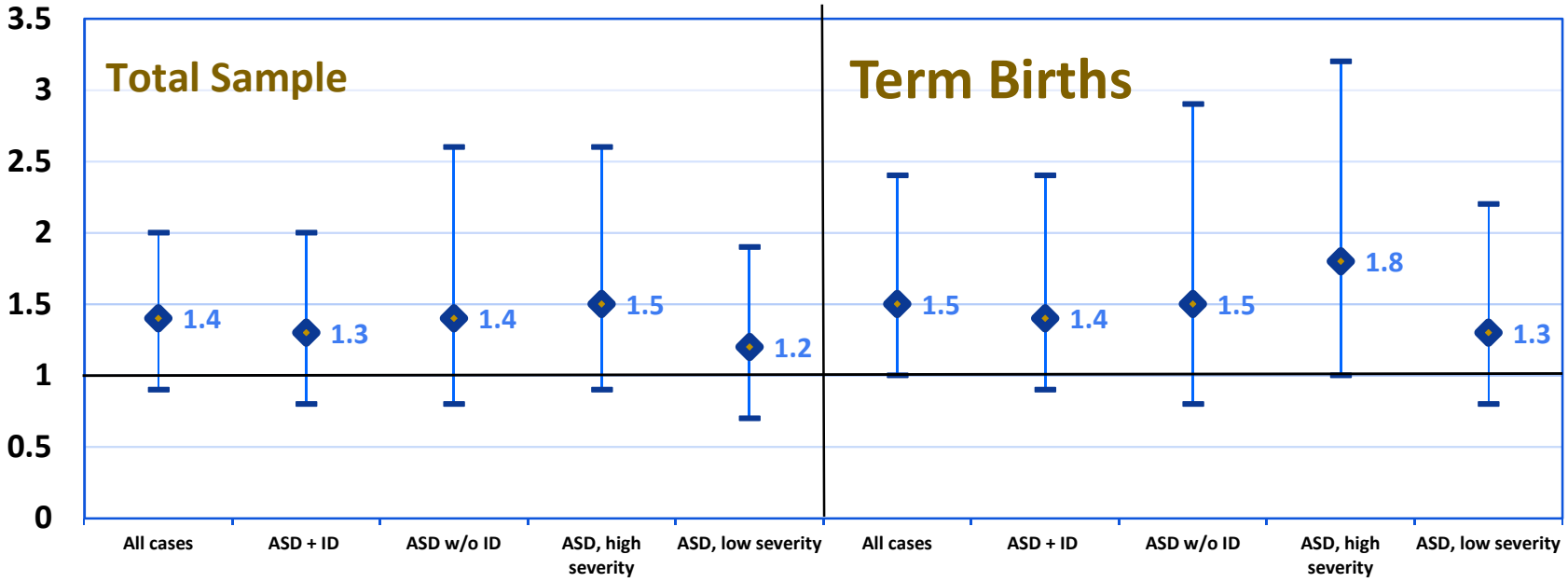
- Odds ratios derived from multivariable logistic regression
  - adjusted for child sex, maternal age, education, race-ethnicity
- Analyses run for total sample and sample limited to children born at term (37 or more weeks gestation) to eliminate competing risks caused by preterm birth
- Several factors possibly related to the underlying mechanism also assessed

Adjusted odds ratios and 95% confidence intervals: *Association between ASD and inter-pregnancy interval <18 months*



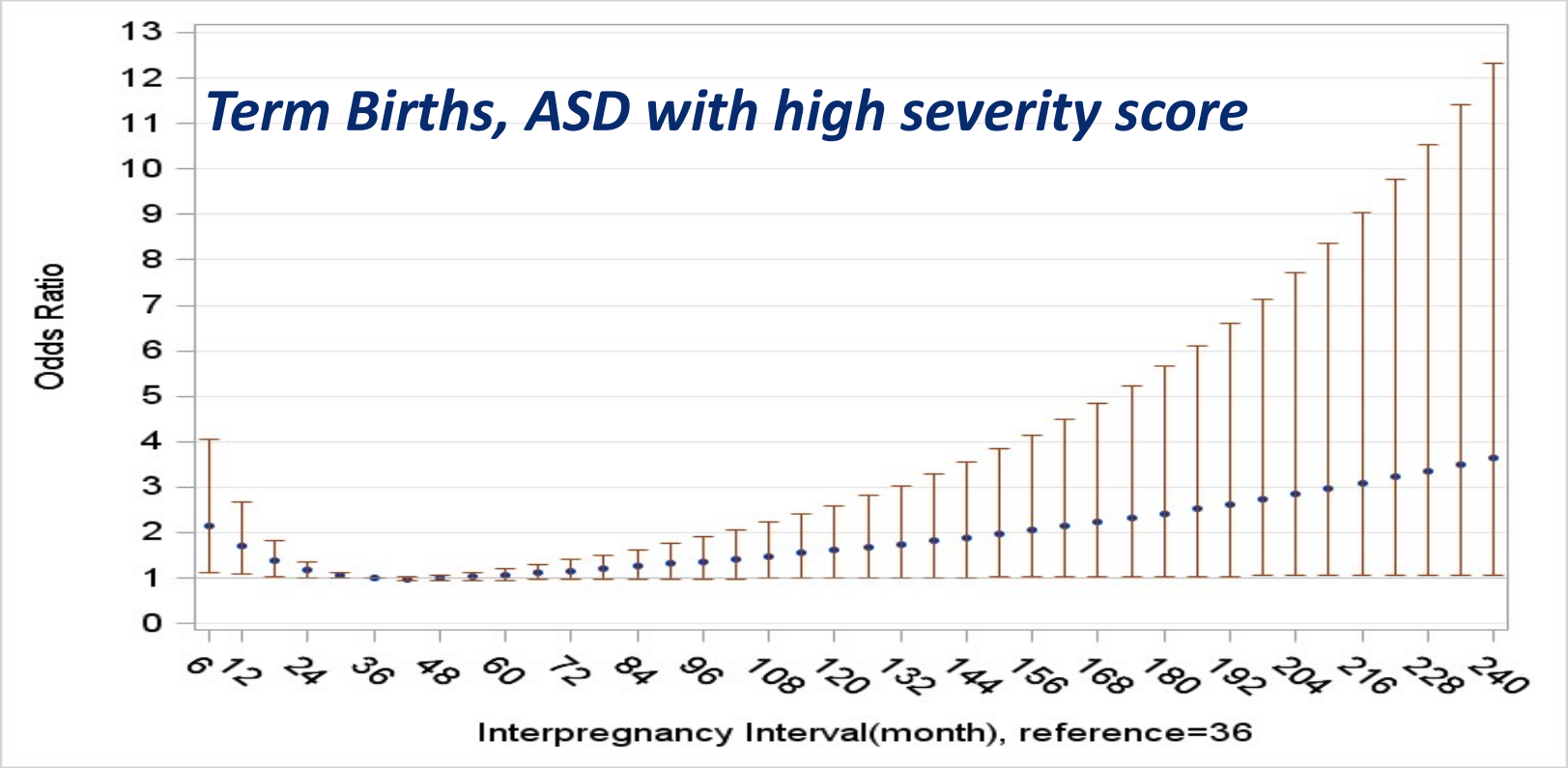
- Modest association between ASD and short birth spacing
- Slightly more pronounced among term births
- Much more pronounced among ASD cases with high ASD symptom severity

Adjusted odds ratios and 95% confidence intervals: *Association between ASD and inter-pregnancy interval ≥60 months*



- Modest association between ASD and long birth spacing
- Slightly more pronounced among term births
- Much more pronounced among ASD cases with high ASD symptom severity

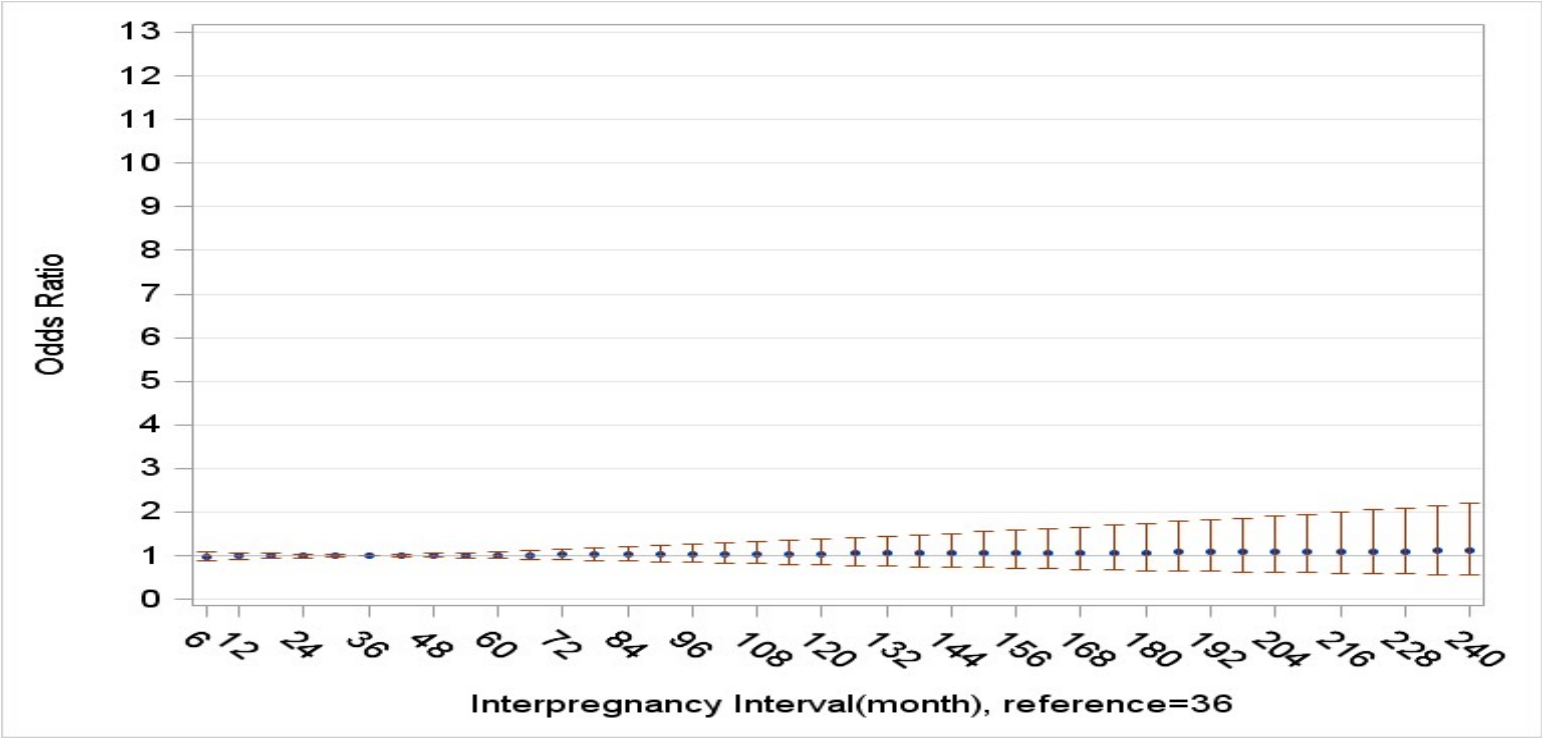
Cubic spline analysis demonstrating a U-shaped association between ASD and inter-pregnancy interval



Further analyses indicated associations were NOT explained by:

- Unplanned pregnancy
- Maternal infertility disorders
- Maternal complications during pregnancy – hypertension, diabetes

Cubic spline analysis demonstrating no association between other DDs and inter-pregnancy interval



Conclusion

- ASD is associated with both short and long birth spacing, particularly ASD with the highest symptom severity
- Association not explained by unplanned pregnancy, mother's underlying infertility disorders, or hypertension or diabetes during pregnancy
- Two areas to investigate further are maternal nutrition and inflammation

Many thanks to all the families who participated in SEED and made this work possible!

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Maternal infection and fever during pregnancy and risk of autism spectrum disorders: findings from the Study to Explore Early Development (SEED)

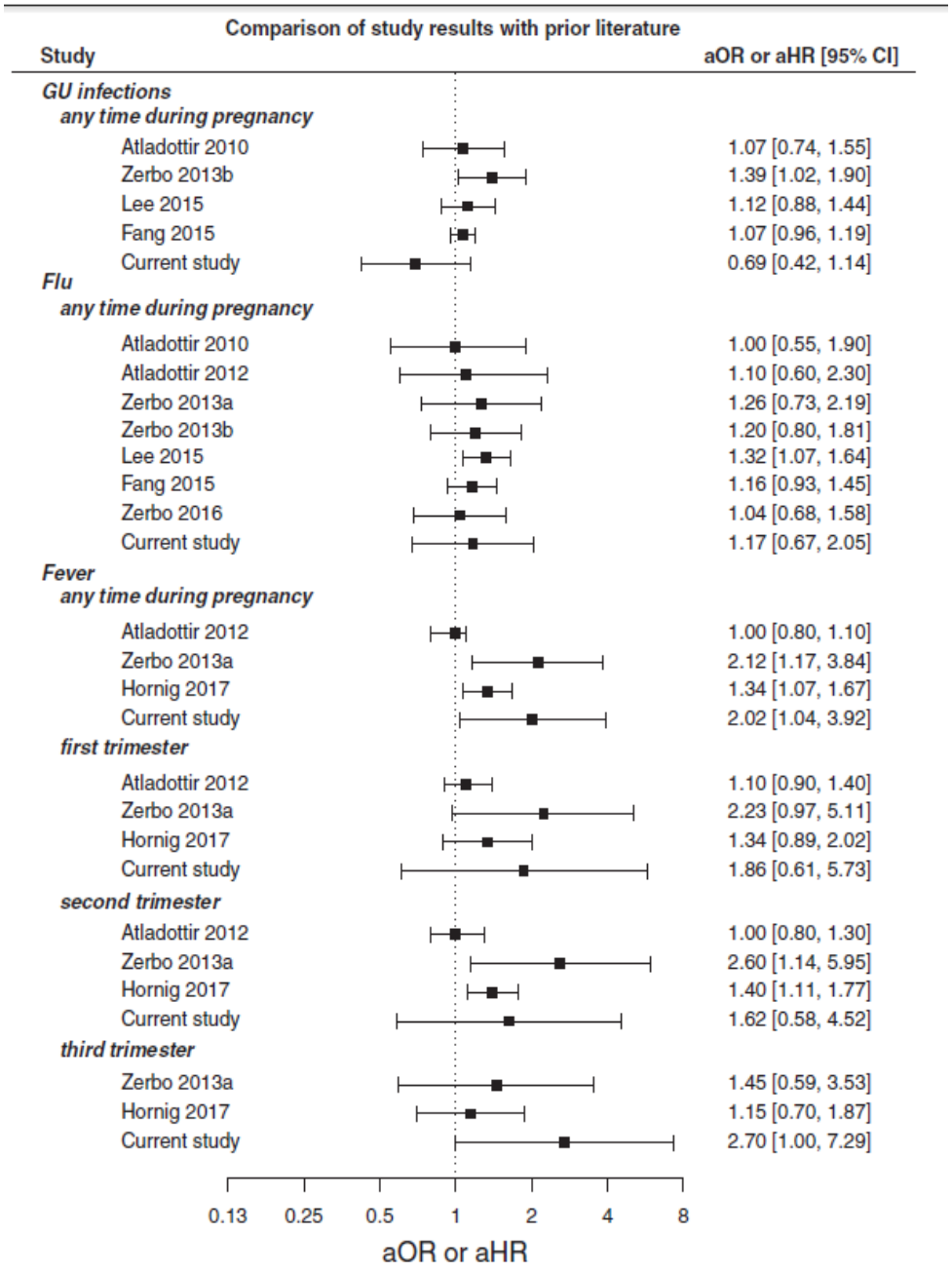
Lisa A. Croen, Yinge Qian, Paul Ashwood, Ousseny Zerbo, Diana Schendel, Jennifer Pinto-Martin, Susan Levy, Laura A. Schieve, Daniele Fallin, Marshalyn Yeargin-Allsopp, Katherine R. Sabourin

Inter-Agency Autism Coordinating Committee Meeting

October 24, 2017

Background

- Maternal infection among the earliest suggested non-genetic risk factors (e.g. rubella exposure, measles/mumps, CMV)
- Influenza findings inconsistent
- Fever findings more consistent, but
  - Different timing (which trimester)
  - Difficult to disentangle fever vs infectious agent



Methods

- **Design**: SEED 1 National case-control study
- Ages 2-5, born 2003 – 2006
- 690 ASD, 1016 DD, 972 POP

- **Exposure Source:**
  - ➢ Caregiver interview
    - 36 specific infections
    - @ -3mo through birth
      - Medications
      - Fever
  - ➢ L&D Medical Record
    - Infections, medications, fever

- **Exposure definitions:**
  - Any infection
  - Organism type
  - Organ affected
  - Timing by trimester

Results 1: Maternal infection during pregnancy, by organ system and organism, SEED, 2003-2006 births

Maternal infection	ASD (N=606)	DD (N=856)	POP (N=796)	ASD vs POP	DD vs POP
	N (%)	N (%)	N (%)	p-Value	p-Value
Any Infection	367 (60.56)	504 (58.88)	470 (59.05)	0.58	0.96
Organ System					
Cardiovascular	1 (0.17)	0 (0.00)	1 (0.13)	1.00	
Skin	11 (1.82)	15 (1.57)	6 (0.75)	0.09	0.08
Eye	5 (0.83)	4 (0.47)	6 (0.75)	1.00	0.54
GI	17 (2.81)	32 (3.74)	24 (3.02)	0.87	0.50
Lower Respiratory	6 (0.99)	11 (1.29)	6 (0.75)	0.77	0.34
Other Respiratory	144 (23.76)	217 (25.35)	201 (25.25)	0.53	1.00
Genitourinary	**191 (31.52)**	244 (28.50)	**210 (26.38)**	**0.04**	0.35
Other Organ	25 (4.13)	35 (4.09)	29 (3.64)	0.68	0.70
Unknown Organ	**189 (31.19)**	206 (20.07)	**198 (24.87)**	**0.01**	0.73
Organism					
Bacteria	**220 (36.30)**	264 (30.84)	**249 (31.28)**	**0.05**	0.87
Virus	82 (13.53)	114 (13.32)	104 (13.07)	0.81	0.88
Fungus	82 (13.53)	101 (11.80)	90 (11.31)	0.22	0.76
Parasite	9 (1.49)	20 (2.34)	11 (1.38)	1.00	0.20
Unknown	188 (31.22)	269 (31.43)	244 (30.65)	0.91	0.75

Results 2: Maternal infection by timing during pregnancy and risk of ASD and DD, SEED, 2003-2006 births

Trimester	ASD (N=606)	DD (N=856)	POP (N=796)	ASD vs POP			DD vs POP		
	N (%)	N (%)	N (%)	Crude OR (95% CI)	ORadj1 (95% CI)	ORadj2 (95% CI)	Crude OR (95% CI)	ORadj1 (95% CI)	ORadj2 (95% CI)
Any Infection									
T0	76	73	62	**1.70**	**1.58**	**1.73**	1.10	0.98	0.91
	(12.5)	(8.5)	(7.8)	**(1.2-2.4)**	**(1.05-2.37)**	**(1.03-2.93)**	(.08-1.57)	(0.65-1.46)	(0.53-1.57)
T1	174	227	203	1.18	1.19	1.09	1.05	0.99	0.93
	(28.71)	(26.52)	(25.50)	(0.93-1.49)	(0.90-1.56)	(0.79-1.50)	(0.85-1.31)	(0.77-1.28)	(0.69-1.25)
T2	187	260	221	1.16	1.02	0.87	1.14	0.88	0.81
	(30.86)	(30.37)	(27.76)	(0.92-1.46)	(0.78-1.33)	(0.65-1.17)	(0.92-1.40)	(0.69-1.13)	(0.62-1.06)
T3	252	308	311	1.11	1.04	1.11	0.88	**0.74**	0.83
	(41.58)	(35.98)	(39.07)	(0.90-1.38)	(0.81-1.33)	(0.84-1.45)	(0.72-1.07)	**(0.59-0.93)**	(0.65-1.06)
Pregnancy	367	504	470	1.07	1.02	0.94	0.99	0.84	0.80
	(60.6)	(58.9)	(59.0)	(0.86-1.3)	(0.79-1.31)	(0.68-1.31)	(0.81-1.2)	(0.67-1.05)	(0.59-1.08)

ORadj1 = adjusted by child sex, maternal age, maternal race, maternal education, income during pregnancy, maternal psych disease hx, hypertension, site

ORadj2 = adjusted by child sex, maternal age, maternal race, maternal education, income during pregnancy, maternal psych disease hx, hypertension, site, any medication for infection

Results 3: Maternal infection with and without fever by timing during pregnancy and risk of ASD, SEED, 2003-2006 births

	ASD	DD	POP	ASD vs POP		
	N (%)	N (%)	N (%)	Crude OR (95% CI)	ORadj1 (95% CI)	ORadj2 (95% CI)
Any Infection with Fever						
T0	11 (2.03)	4 (0.51)	7 (0.94)	2.18 (0.84-5.65)	2.11 (0.68-6.58)	-
T1	20 (4.42)	16 (2.48)	25 (4.05)	1.10 (0.60-2.00)	0.91 (0.46-1.79)	0.87 (0.32-2.40)
T2	31 (6.89)	38 (5.99)	21 (3.52)	**2.03 (1.15-3.58)**	**2.19 (1.14-4.23)**	**2.05 (0.95-4.45)**
T3	30 (7.81)	48 (8.05)	44 (8.32)	0.93 (0.58-1.52)	0.80 (0.45-1.40)	1.04 (0.56-1.93)
Pregnancy	73 (23.40)	92 (20.72)	86 (20.87)	1.16 (0.81-1.65)	1.08 (0.71-1.62)	0.95 (0.45-1.98)
Any Infection without Fever						
T0	65 (10.92)	69 (8.10)	55 (6.97)	**1.64 (1.12-2.33)**	1.51 (0.98-2.31)	**1.72 (1.01-2.94**)
T1	154 (26.28)	211 (25.12)	178 (23.09)	1.19 (0.93-1.52)	1.23 (0.92-1.64)	1.16 (0.84-1.62)
T2	156 (27.13)	222 (27.14)	200 (25.81)	1.07 (0.84-1.37)	0.92 (0.69-1.22)	0.83 (0.61-1.12)
T3	222 (38.45)	260 (32.18)	267 (35.51)	1.14 (0.91-1.43)	1.07 (0.83-1.38)	1.13 (0.85-1.49)
Pregnancy	294 (55.16)	412 (53.93)	384 (54.08)	1.04 (0.83-1.31)	1.01 (0.78-1.31)	0.96 (0.68-1.36)

Summary

- Maternal infection during pregnancy was relatively common, occurring in approximately 60% of all women.
- Risk of ASD was increased only among:
  - Women with infection accompanied by fever during the second trimester
  - Women with infection without fever during the three months prior to conception
  - After controlling for several covariates including treatment with medication
- By contrast, neither maternal infection with or without fever was associated with DD
- Growing evidence of fever-based associations

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nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-00868-y OPEN

Cross-tissue integration of genetic and epigenetic data offers insight into autism spectrum disorder

Shan V. Andrews[1,2], Shannon E. Ellis[3], Kelly M. Bakulski[4], Brooke Sheppard[1,2], Lisa A. Croen[5], Irva Hertz-Picciotto[6,7], Craig J. Newschaffer[8,9], Andrew P. Feinberg[10,11], Dan E. Arking[2,3], Christine Ladd-Acosta[1,2,10] & M. Daniele Fallin[2,10,12]

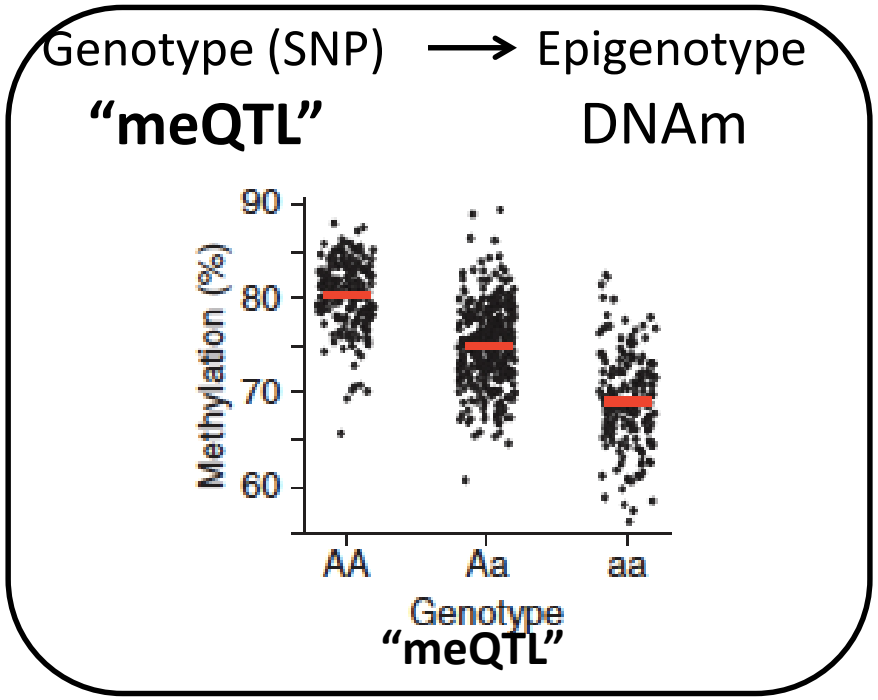
Inter-Agency Autism Coordinating Committee Meeting

October 24, 2017

What can we learn by integrating ASD genetic and epigenetic information?

Background:

- Epigenetic variation contributes to gene regulation/expression
- Epigenetic variation is tissue and timing dependent
- Epigenetic variation is in part controlled by genetic variation



Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis

Yun Liu[1,2,12], Martin J Aryee[1,3,12], Leonid Padyukov[4,5,12], M Daniele Fallin[1,6,7,12], Espen Hesselberg[4,5], Arni Runarsson[1,2], Lovisa Reinius[8], Nathalie Acevedo[9], Margaret Taub[1,6], Marcus Ronninger[4,5], Klementy Shchetynsky[4,5], Annika Scheynius[9], Juha Kere[8], Lars Alfredsson[10], Lars Klareskog[4,5], Tomas J Ekström[5,11] & Andrew P Feinberg[1,2,6]

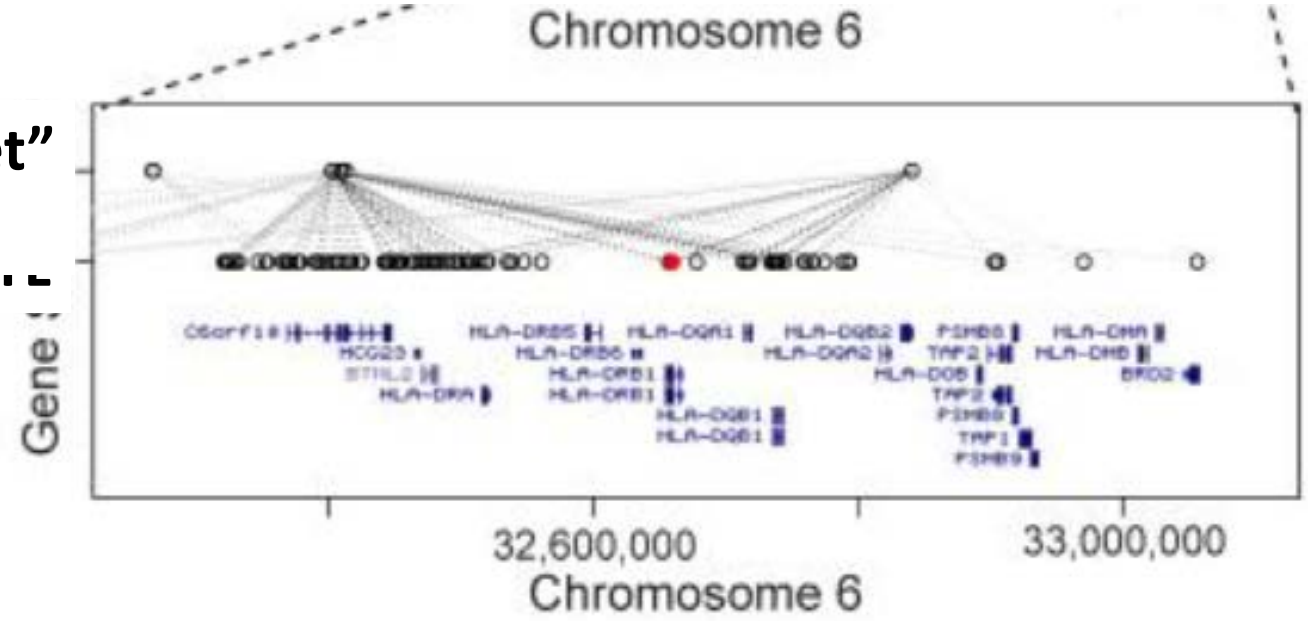
nature biotechnology

What can we learn by integrating ASD genetic and epigenetic information?

Background:

- Epigenetic variation contributes to gene regulation/expression
- Epigenetic variation is tissue and timing dependent
- Epigenetic variation is in part controlled by genetic variation
  - **Genetic-epigenetic "maps"** can be created, by tissue

meQTL "target"

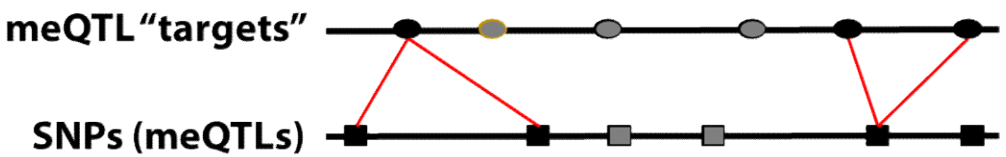


meQTL "Maps" Across Tissues

- From joint genotype and methylation data of
  - Peripheral blood (discovery in **SEED**, 2-5 yo)
  - Cord blood (discovery in **EARLI**, birth)
  - Fetal Brain (Mill, published list)

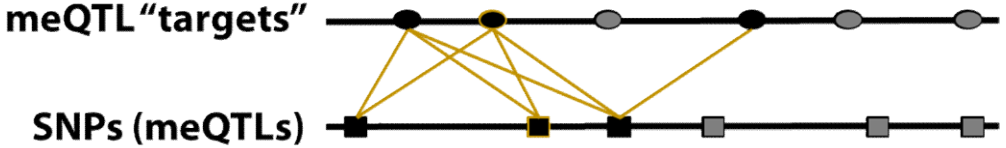
Child blood

Genotype → Epigenotype



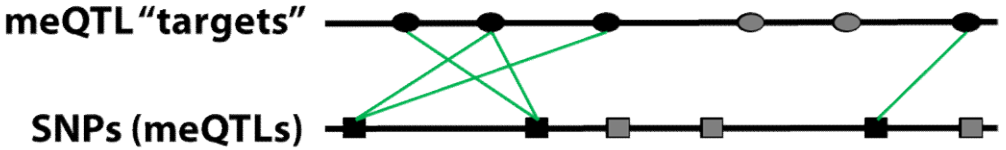
Cord (infant) blood

Genotype → Epigenotype



Fetal brain tissue

Genotype → Epigenotype



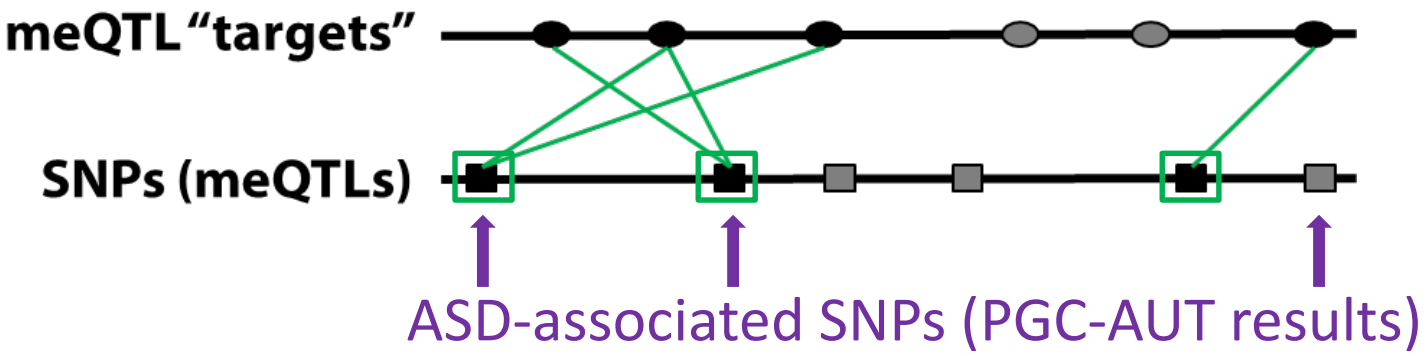
What can we learn by integrating ASD genetic and epigenetic information?

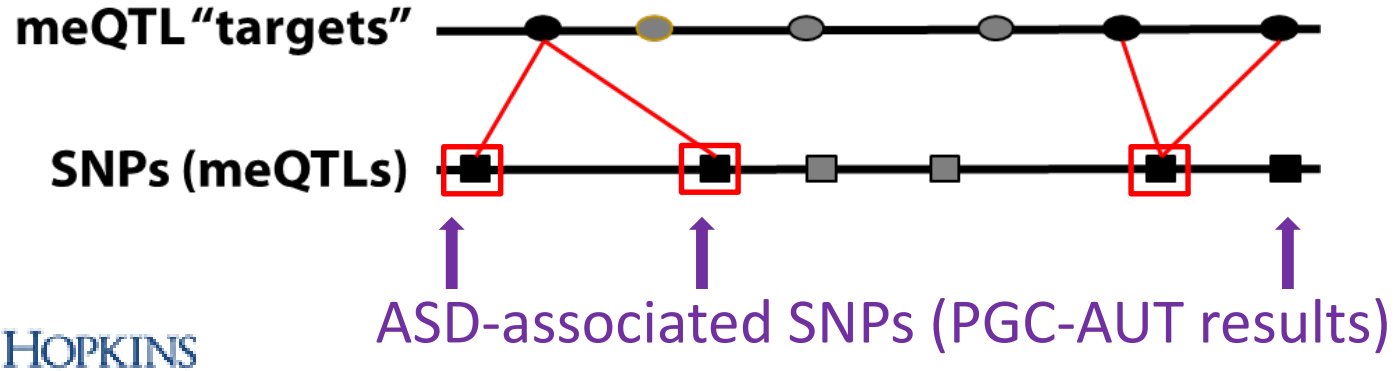
What can we learn using meQTL information?

1. Are ASD-associated SNPs enriched for meQTLs for particular tissues including blood?
2. Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?
3. Do ASD-associated SNP meQTL targets point to genes not previously implicated?

What can we learn using meQTL information?

1. **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?**





What can we learn using meQTL information?

1. **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?**
   - ✓ YES

	ASD *P* value = 1e-03		
	meQTL *P*-value = 1e-08		
Fetal brain[a]		1.70 (<0.001)	
	meQTL FDR = 10%	meQTL FDR = 5%	meQTL FDR = 1%
Peripheral blood[b]	1.22 (<0.001)	1.20 (<0.001)	1.23 (<0.001)
Cord blood[b]	1.14 (0.032)	1.21 (0.011)	1.20 (0.023)
Lung[a]	—	1.09 (0.343)	—

Enrichment fold statistics and *P* values based on 1000 permutations
[a]LD pruning performed with 1000 Genomes CEU samples
[b]LD pruning performed with the study-specific genotype data. See Methods for additional details

What can we learn in autism using meQTL information?

1. Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?
   - ✓ YES

Table 2 Enrichment statistics for meQTLs derived from 4 tissue types in ASD GWAS SNPs

	ASD *P* value = 1e-03			ASD *P* value = 1e-04		
	meQTL *P*-value = 1e-08			meQTL *P* value = 1e-08		
Fetal brain[a]		1.70 (<0.001)			3.55 (<0.001)	
	meQTL FDR = 10%	meQTL FDR = 5%	meQTL FDR = 1%	meQTL FDR = 10%	meQTL FDR = 5%	meQTL FDR = 1%
Peripheral blood[b]	1.22 (<0.001)	1.20 (<0.001)	1.23 (<0.001)	1.31 (0.001)	1.40 (<0.001)	1.58 (<0.001)
Cord blood[b]	1.14 (0.032)	1.21 (0.011)	1.20 (0.023)	1.13 (0.299)	1.10 (0.392)	1.10 (0.406)
Lung[a]	—	1.09 (0.343)	—	—	0.80 (0.301)	—

Enrichment fold statistics and *P* values based on 1000 permutations
[a]LD pruning performed with 1000 Genomes CEU samples
[b]LD pruning performed with the study-specific genotype data. See Methods for additional details

What can we learn using meQTL information?

- ✓ **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?** YES
2. **Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?**

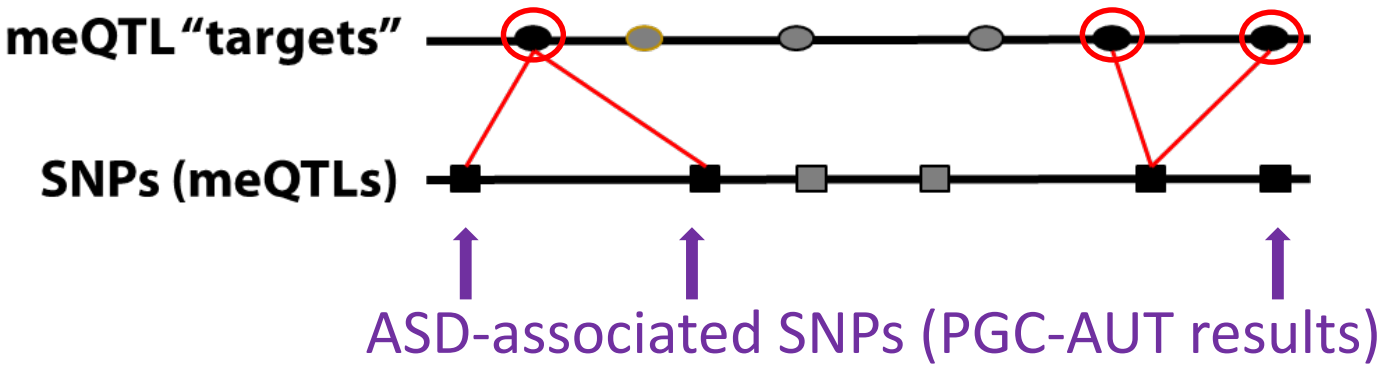


Table 3 Gene Ontology terms significantly enriched in multiple tissue types in comparison of ASD-related meQTL targets to meQTL targets generally

Term	Peripheral blood scaled rank[a]	Cord blood scaled rank[a]	Fetal brain scaled rank[a]
Response to interferon-gamma	0.14	0.11	0.11
Positive regulation of relaxation of cardiac muscle	0.20	0.46	0.30
Production of molecular mediator of immune response	0.65	0.22	0.28
Cellular response to interferon-gamma	NA	0.07	0.09
Detection of bacterium	NA	0.18	0.06
Detection of biotic stimulus	NA	0.26	0.04
T-helper 1 type immune response	NA	0.08	0.34
Regulation of interleukin-10 secretion	NA	0.09	0.43
Interferon-gamma production	NA	0.57	0.19
Regulation of interleukin-4 production	NA	0.24	0.62
Interleukin-4 production	NA	0.29	0.60
Interleukin-10 production	NA	0.25	0.74
Tongue development	NA	0.68	0.32
Inflammatory response to antigenic stimulus	NA	0.32	0.81
Endochondral bone growth	NA	0.71	0.53
Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II	0.01	0.05	NA
T-cell costimulation	0.05	0.01	NA
Positive regulation of hormone secretion	0.09	0.04	NA
Antigen receptor-mediated signaling pathway	0.08	0.13	NA
Immunoglobulin production involved in immunoglobulin mediated immune response	0.24	0.03	NA
Single organismal cell-cell adhesion	0.23	0.12	NA
Single organism cell adhesion	0.34	0.16	NA
Negative regulation of nonmotile primary cilium assembly	0.16	0.39	NA
Antigen processing and presentation of polysaccharide antigen via MHC class II	0.02	0.58	NA

What can we learn using meQTL information?

- ✓ **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?** YES
- 2. **Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?**
  - ✓ YES - Blood, Cord blood, and Fetal Brain ASD meQTL targets implicate the <u>immune system</u>
  - Consistent with ASD findings to date:
    - Genetic variation does not (generally) point to immune system
    - Expression (and now methylation) results do, as well as many epidemiologic findings

Immune System Implicated by Expression and Methylation

Brain Studies

Blood Studies

Gene Expression

ARTICLE

Received 28 Sep 2014 | Accepted 3 Nov 2014 | Published 10 Dec 2014 DOI: 10.1038/ncomms6748 OPEN

Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism

Simone Gupta[1], Shannon E. Ellis[1], Foram N. Ashar[1], Anna Moes[1], Joel S. Bader[1,2], Jianan Zhan[2], Andrew B. West[3] & Dan E. Arking[1]

Transcriptomic analysis of autistic brain reveals convergent molecular pathology

Irina Voineagu[1], Xinchen Wang[2], Patrick Johnston[3], Jennifer K. Lowe[1], Yuan Tian[1], Steve Horvath[4], Jonathan Mill[3], Rita M. Cantor[4], Benjamin J. Blencowe[2] & Daniel H. Geschwind[1,4]

Peripheral blood gene expression signature differentiates children with autism from unaffected siblings

S. W. Kong · Y. Shimizu-Motohashi · M. G. Campbell · I. H. Lee · C. D. Collins · S. J. Brewster · I. A. Holm · L. Rappaport · I. S. Kohane · L. M. Kunkel

RESEARCH ARTICLE

Transcriptome Profiling of Peripheral Blood in 22q11.2 Deletion Syndrome Reveals Functional Pathways Related to Psychosis and Autism Spectrum Disorder

Maria Jalbrzikowski[1], Maria T. Lazaro[2], Fuying Gao[1], Alden Huang[2], Carolyn Chow[1], Daniel H. Geschwind[1,3], Giovanni Coppola[1,3☯], Carrie E. Bearden[1,4☯*]

DNA Methylation

ORIGINAL ARTICLE

DNA methylation analysis of the autistic brain reveals multiple dysregulated biological pathways

S Nardone, D Sharan Sams, E Reuveni, D Getselter, O Oron, M Karpuj and E Elliott

What can we learn using meQTL information?

- ✓ **Are ASD-associated SNPs enriched for meQTLs <u>for particular tissues</u> including blood?** YES
- ✓ **Do ASD-associated SNP meQTL targets (CpGs) point to particular biology?** Immune system
3. **Do ASD-associated SNP meQTL targets point to genes not previously implicated?**

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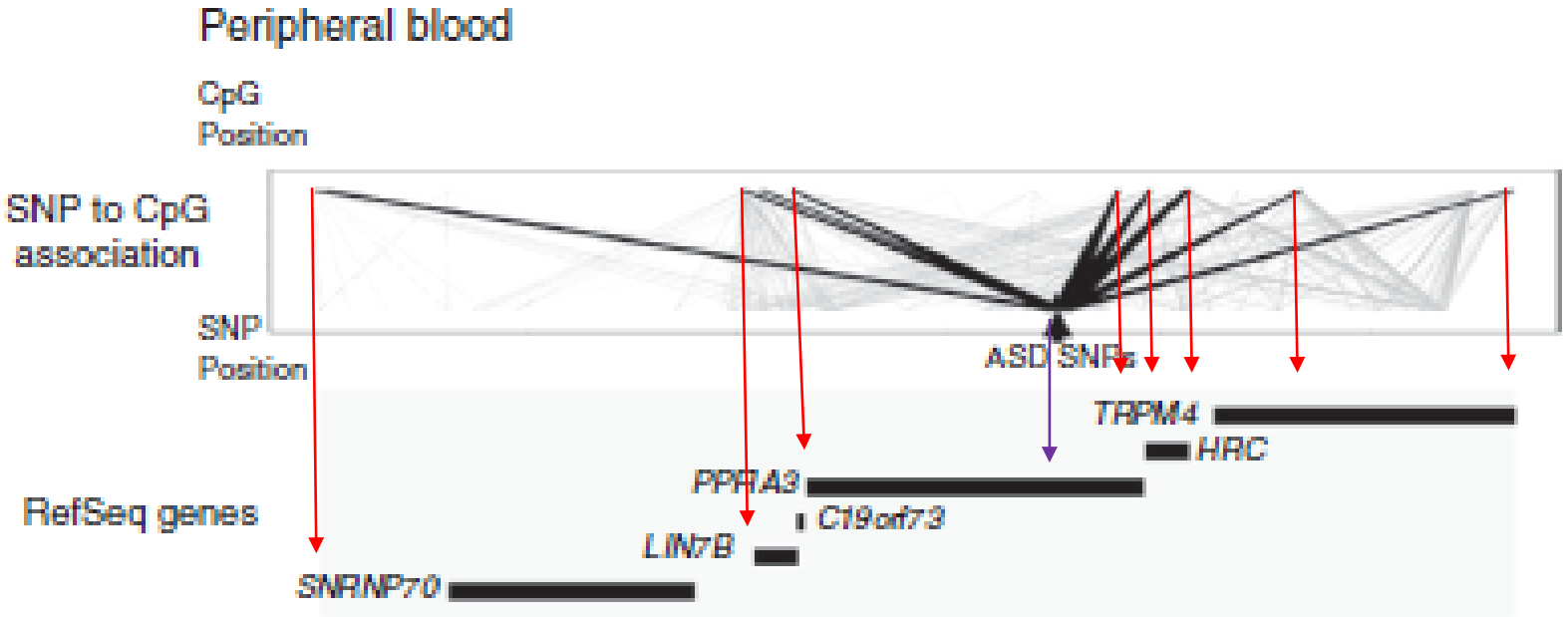

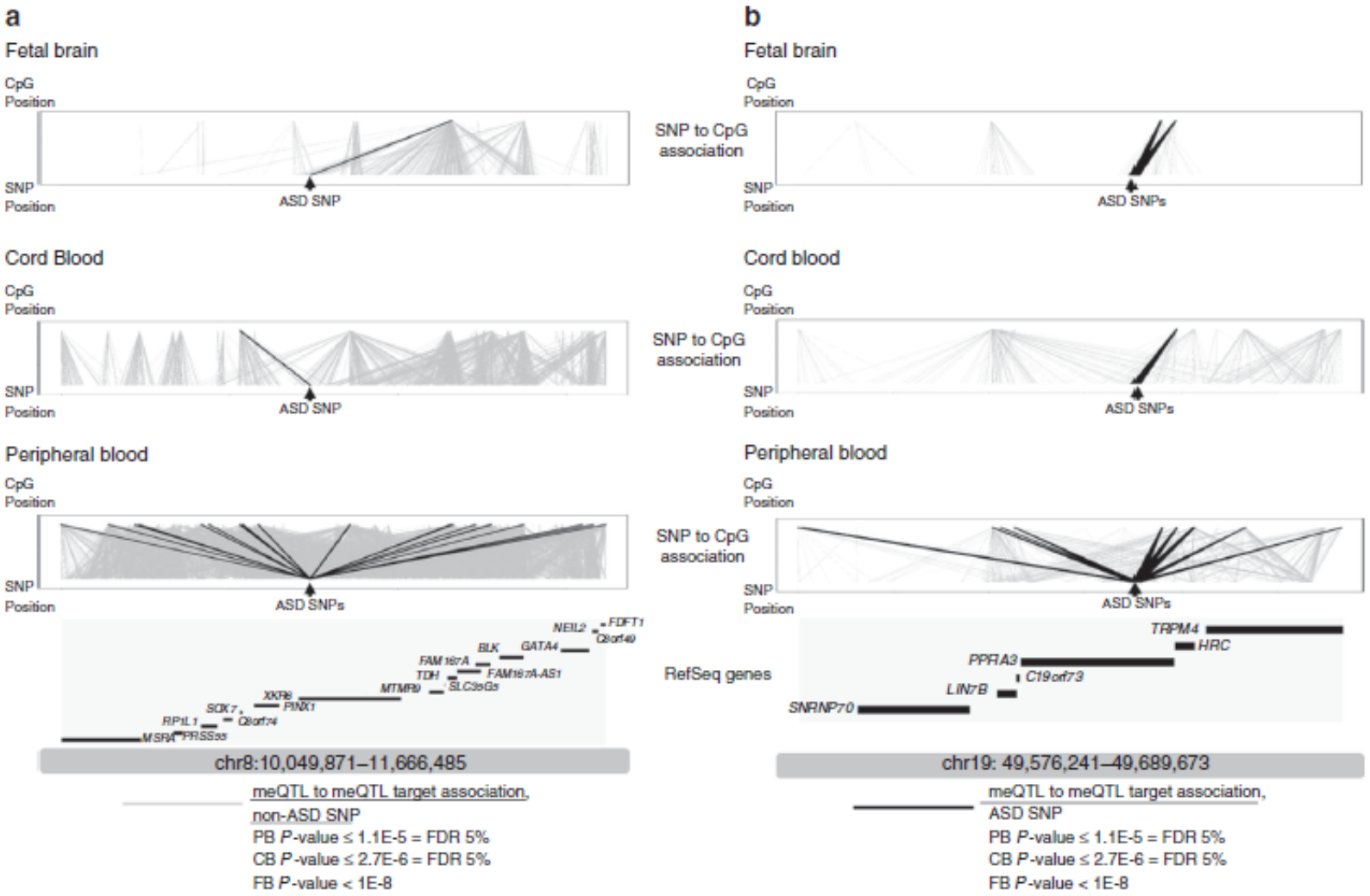

Fig. 1 'Expansion' of ASD loci through meQTL mapping in peripheral blood, cord blood, and fetal brain. Each tissue-specific panel presents, from bottom to top: genomic location, gene annotations, SNP locations, SNP–CpG associations, CpG locations. *Light gray* meQTL association lines denote all SNP to CpG associations in that tissue type; *Dark* meQTL association lines denote SNP–CpG associations for ASD-associated SNPs in PGC (*P* value < = 1e–04). **a** Locus at chr8; **b** Locus at chr19. Data are presented for meQTL maps for fetal brain (*top*); cord blood meQTLs (*middle*), and peripheral blood meQTLs (*bottom*). Please note locus coordinates differ from those in Supplementary Data 6 because in this context they encompass the locations of meQTL target CpG sites

What can we learn using meQTL information?

- ✓ **ASD-associated SNPs are enriched for meQTLs <u>for particular tissues</u> including blood?**
- ✓ **ASD-associated SNP meQTL targets (CpGs) point to particular biology**
- ✓ **ASD-associated SNP meQTL targets point to genes not previously implicated**

- ➢ **Blood–based meQTL information pointed to similar conclusions!**
- ❖ *Some important limitations regarding meQTL lists and ASD SNP list*

Summary of SEED I "Omic" Data

SEED 1 Genotype Data							
		# SEED 1 – child			# SEED 1 – mom		
Platform	**# SNPs***	**ASD****	**POP**	**DD**	**ASD**	**POP**	**DD**
Omni-Quad	>1M	419	555	193	0	0	0
Affy axiom KP	>700K	173	176	7	0	0	0
Omni-5M+ exome	>4.5M	13	19	1	301	0	0
Illumina MEGA	>1.4M	0	0	0		1269***	0
		605	**750**	**201**			

SEED 1 Methylation Data				
Platform	**# CpGs**	**ASD****	**POP**	**DD**
Illumina 450K	455,664	455	515	0

* measured. Imputed SNP ~ 8M

** includes possible low functioning cases (n=6)

*** genotype cleaning in-progress; numbers could change slightly

Collaborative Projects To Date

3 ASD GWAS contributions (meta-analysis and replication)
3 ASD EWAS contributions (meta-analysis)
2 non-ASD EWAS contributions (meta-analysis, PACE)
2 multi-omic collaborative projects

SEED-only methods contributions (not ASD focused):
2 EWAS / meQTL methodologic contributions
1 smoking environmental biomarker paper

Research Group

Chris Ladd-Acosta
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Johns Hopkins Biosample Repository

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CENTER FOR EPIGENETICS
INSTITUTE FOR BASIC BIOMEDICAL SCIENCES

ABOUT THE CENTER / CEGS

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Martin Aryee
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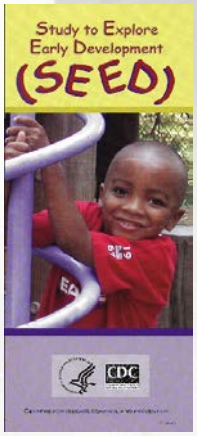
EARLI
Early Autism Risk Longitudinal Investigation

Craig Newschaffer (Network PI)
Lisa Croen (CA PI)
Irva Hertz-Picciotto (UCMIND PI)



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Susan Levy (PA PI)
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Gastrointestinal Symptoms in 2- to 5-Year-Old Children

Interagency Autism Coordinating Committee

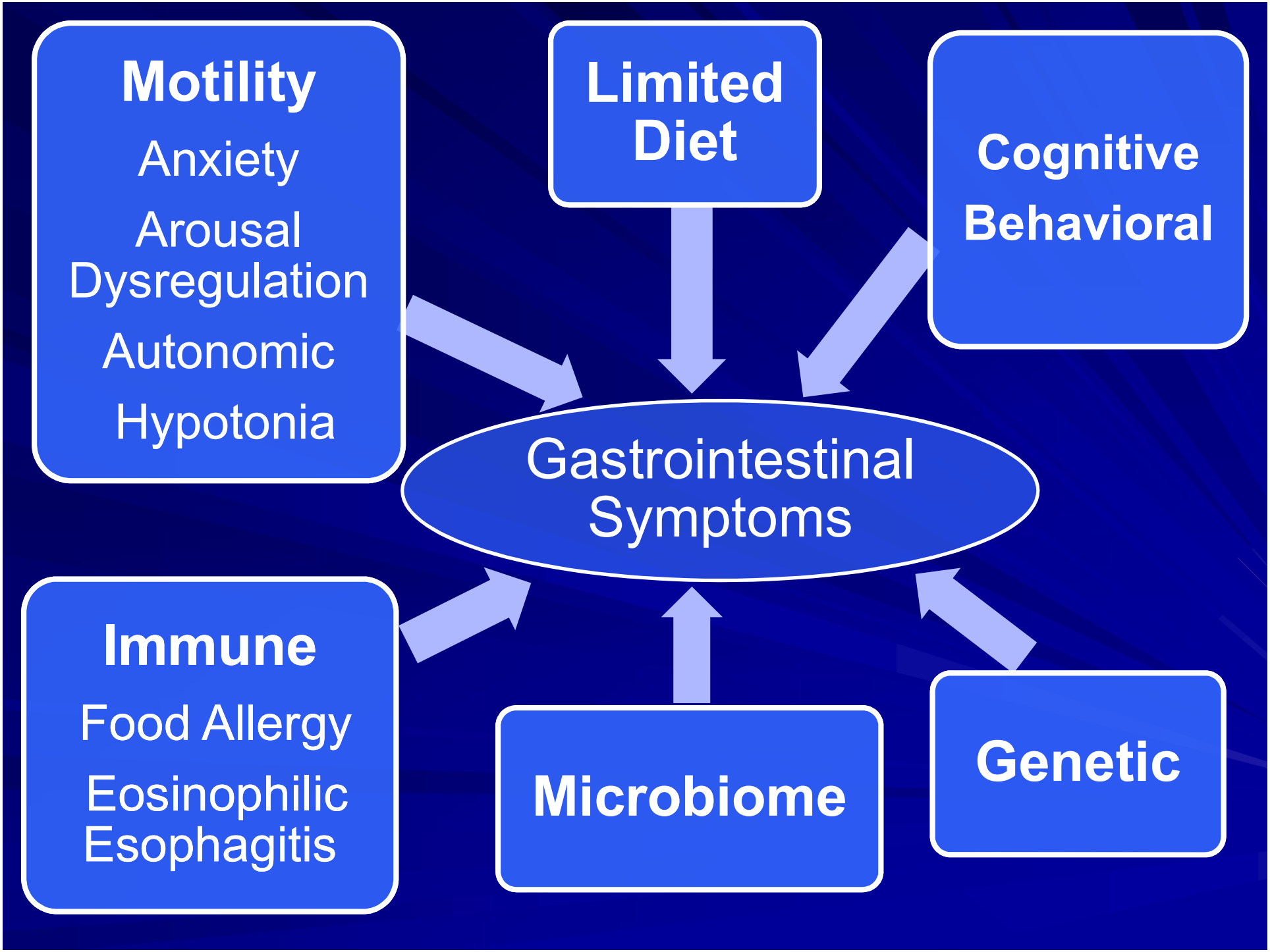
Full Committee Meeting

Ann Reynolds, MD
University of Colorado School of Medicine

October 24, 2017

Gastrointestinal Symptoms (GIS) in ASD

- Questions
  - Prevalence ranges from 9-70%
  - Etiology
  - Phenotypic subtype
- Needs
  - Diverse, non-clinic based sample
  - Large sample with comparison groups
  - Well characterized sample


Motility
Anxiety
Arousal Dysregulation
Autonomic
Hypotonia
Limited Diet
Cognitive Behavioral
Gastrointestinal Symptoms
Immune
Food Allergy
Eosinophilic Esophagitis
Microbiome
Genetic

Methods

- Sample
  - ASD (n=672), DD (n=938), POP (n=851)
  - Stool diary: ASD (n=423), DD (n=551), and POP (n=597)
- GI symptoms
  - Parent Completed Gastrointestinal Questionnaire (yes/no)
  - Stool Diary using Bristol Stool Scale (7 point Likert Scale)
  - GI Medications used in previous month
- Associations with GIS
  - ADOS Calibrated Severity Scale - ASD only
  - ADI-R Regression Questions - ASD only
  - Child Behavior Checklist (CBCL)
  - Children's Sleep Habits Questionnaire (CSHQ)

GI Symptoms Methods

Parent Report

- Any GIS
- Diarrhea
- Loose Stools
- Constipation
- Loose Stool alternating w/constipation
- Vomiting
- Abdominal pain
- Gas

Parent Report Plus Stool Diary

- Stool Consistency
- Stool Frequency
- Laxative or Stool Softener use
- Vomiting
- Abdominal Pain
- Gas

GIS Diagnosis (+/-)

Analysis

- Multivariable logistic regression generalized estimating equation (GEE) models
- All models adjusted for
  - Maternal race/ethnicity, education level, and age at child's birth
  - Child sex and cognitive skills
  - Site

GIS Prevalence in SEED

	ASD	DD	POP	ASD vs DD Adjusted OR (95% CI)	ASD vs POP Adjusted OR (95% CI)
Parent Report Only					
GIS	34.6%	22.1%	12.0%	1.85 (1.54-2.22)*	3.42 (2.11-5.54)*
Parent Report with Stool Diary					
GIS	50.4%	42.6%	30.6%	1.29 (1.07-1.56)**	2.22 (1.56-3.14)*

* p-value < 0.001, ** p-value < 0.05

Association between GIS and regression and autism severity in Children with ASD

- Children with ASD and Regression are 1.5 times more likely to have GIS
  - Adjusted Odds Ratio = 1.53 (95% CI, 1.33-1.77), $p<0.05$
- No Difference in Autism Severity Score in Children with ASD with and without GIS

Association between GIS and behavior

	Mean Difference (95% CI)	p-value
CBCL - Anxious Depressed Subscale		
ASD	0.74(0.22-1.27)	0.0056
DD	0.66(0.31-1)	0.0002
POP	0.73(0.27-1.18)	0.0017
CBCL - Aggressive Behavior Subscale		
ASD	2.35(1.58-3.12)	<.0001
DD	2.87(1.82-3.91)	<.0001
POP	2.13(1.32-2.94)	<.0001

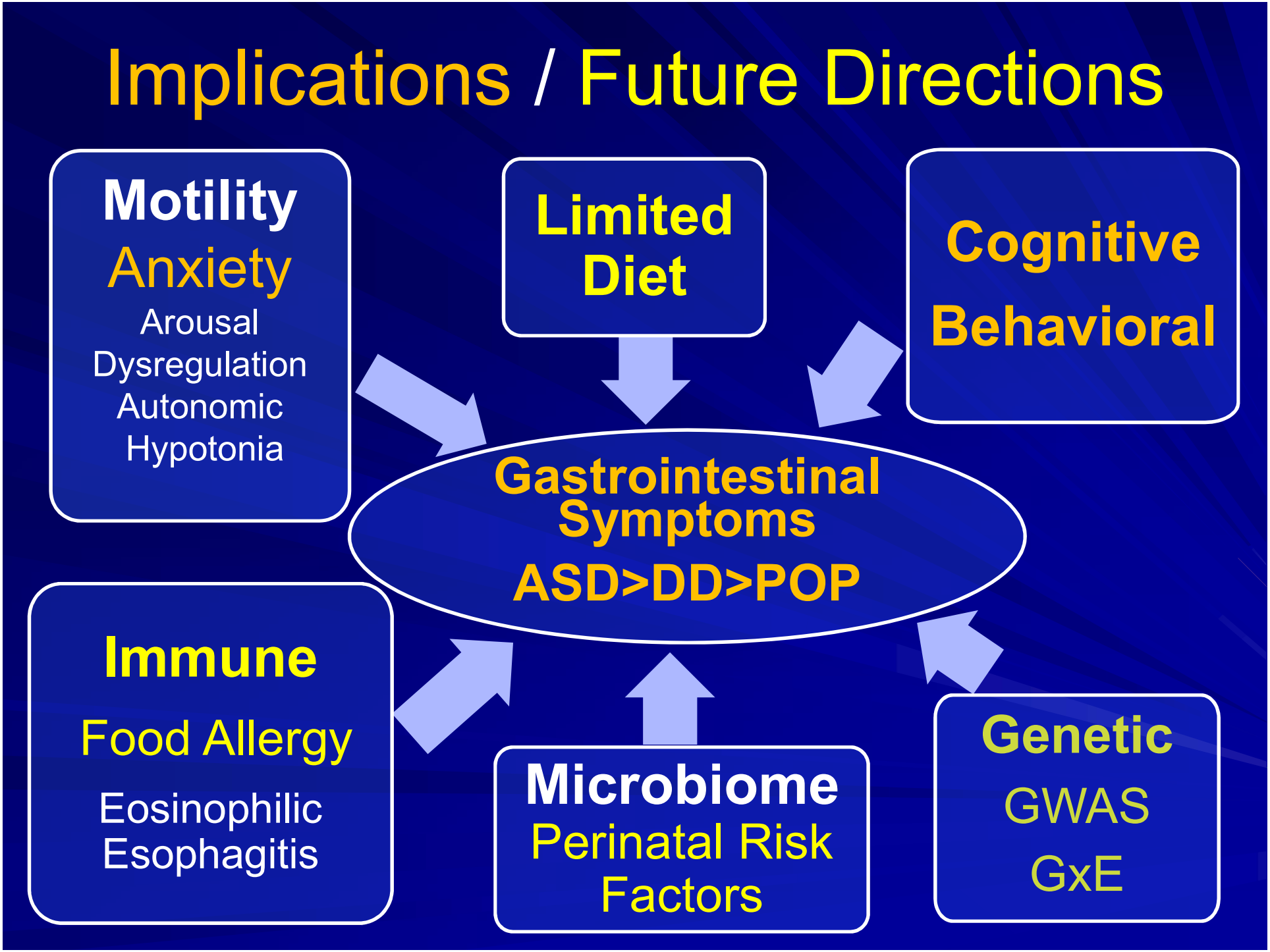
Sleep Concerns and GIS

CSHQ Score > 48		
	OR (95% CI)	p-value
Case	2.07(1.57-2.71)	<0.0001
DD	1.67(1.18-2.36)	0.004
POP	2.08(1.36-3.18)	0.0007

Limitations

- No clinical diagnosis of GIS
- Questionnaire has not been validated
- Stool Diary
  - Differences in demographic variables
  - 51% completed SD during a typical week
  - Children with ASD using treatment for constipation were less likely to have a SD
  - Children with ASD were more likely to use a treatment for constipation other than a laxative or stool softener

Implications / Future Directions



Thank You

- **Children and Their Families**
- **SEED Study Staff**
- **Collaborators**
- University of Colorado Denver
  - **Katherine Sabourin, MPH**
  - Kristina Kaparich, MPH
  - Angela Rachubinski, PhD
- University of Pennsylvania
  - **Susan Levy, MD, MPH**
  - Tanja Kral, PhD
  - Jennifer Pinto-Martin, PhD, MPH
- University of Carolina Chapel Hill
  - Julie Daniels, PhD
- Northern California / Kaiser Permanente
  - Lisa Croen, PhD
- Johns Hopkins Univeristy
  - Daniele Fallin, MD
  - Li-Ching Lee, PhD
- Drexel University
  - Craig Newschaffer, PhD
- Centers for Disease Control and Prevention
  - **Norbert Soke, MD,PhD**
  - Laura Schieve, PhD
  - Lisa Wiggins, PhD
- Michigan State University/DCC
  - Amy Sims
- **CCTSI/CTRC**

Center for Autism and Developmental Disabilities Research and Epidemiology

CADDRE

JFK Partners

UNIVERSITY OF COLORADO

ANSCHUTZ MEDICAL CAMPUS

Children's Hospital Colorado

CCTSI

Colorado Clinical & Translational Sciences Institute

A Novel Protocol for Characterizing Dysmorphology to Enhance the Phenotypic Classification of ASD in the Study to Explore Early Development

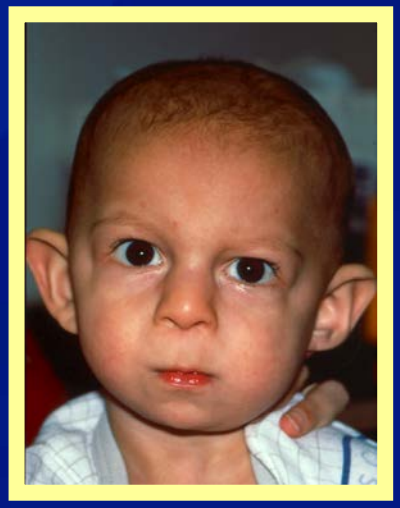
Stuart K. Shapira, MD, PhD
Chief Medical Officer and Associate Director for Science
National Center on Birth Defects and Developmental Disabilities

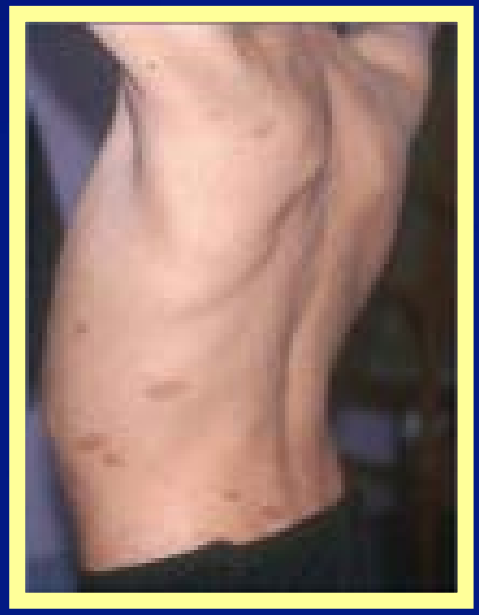
The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.

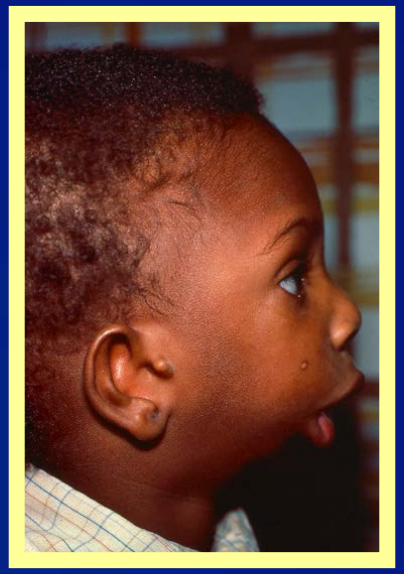
Dysmorphology

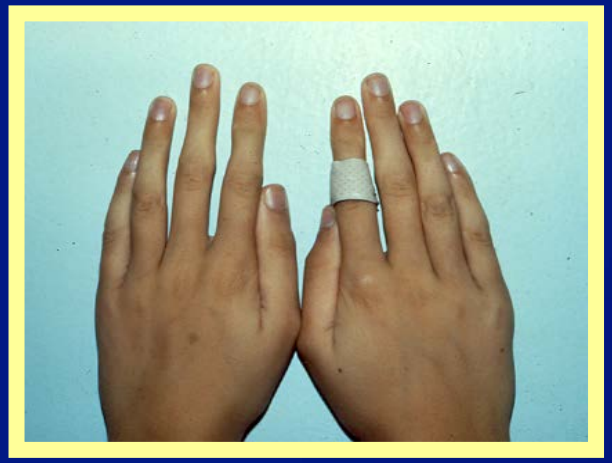
- Dysmorphology is the description of physical features that are dysmorphic
- A physical feature is defined as “dysmorphic” if it
  - Has not followed the normal pattern of growth or formation
  - Is often disproportionate when compared with a “typical” feature
  - Occurs in ≤5% of the general population

Examples of Dysmorphic Features



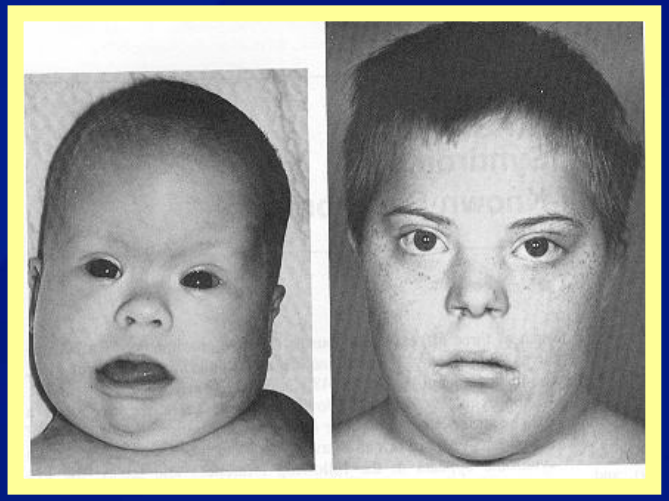






Dysmorphology Provides Clues to Cause

- Relatively flattened face
- Upslanting eyes
- Epicanthal folds
- Prominent tongue
- Small ears
- Redundant neck skin
- Wide spacing between the first and second toes
- Single transverse palmar creases

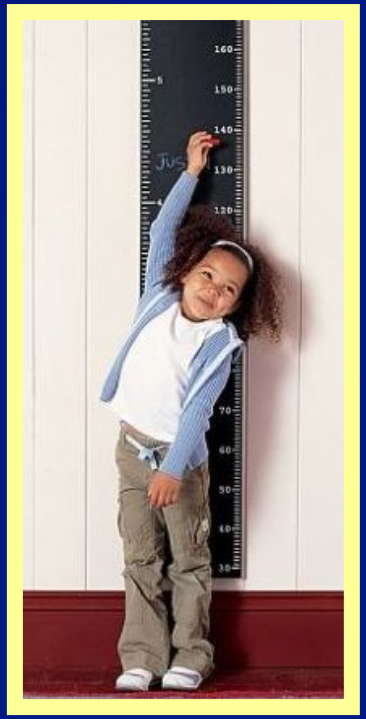


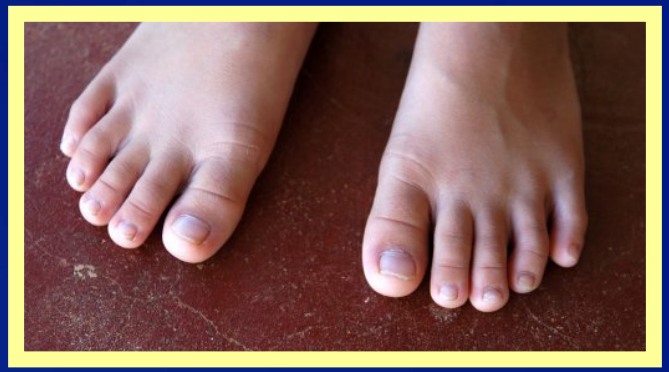
ASD and Dysmorphology

- **Why evaluate dysmorphology for children with ASD?**
- **In children with ASD, the presence of multiple dysmorphic features might**
  - Identify distinctive ASD phenotypes
  - Serve as a potential marker for understanding cause and prognosis

Data Collection

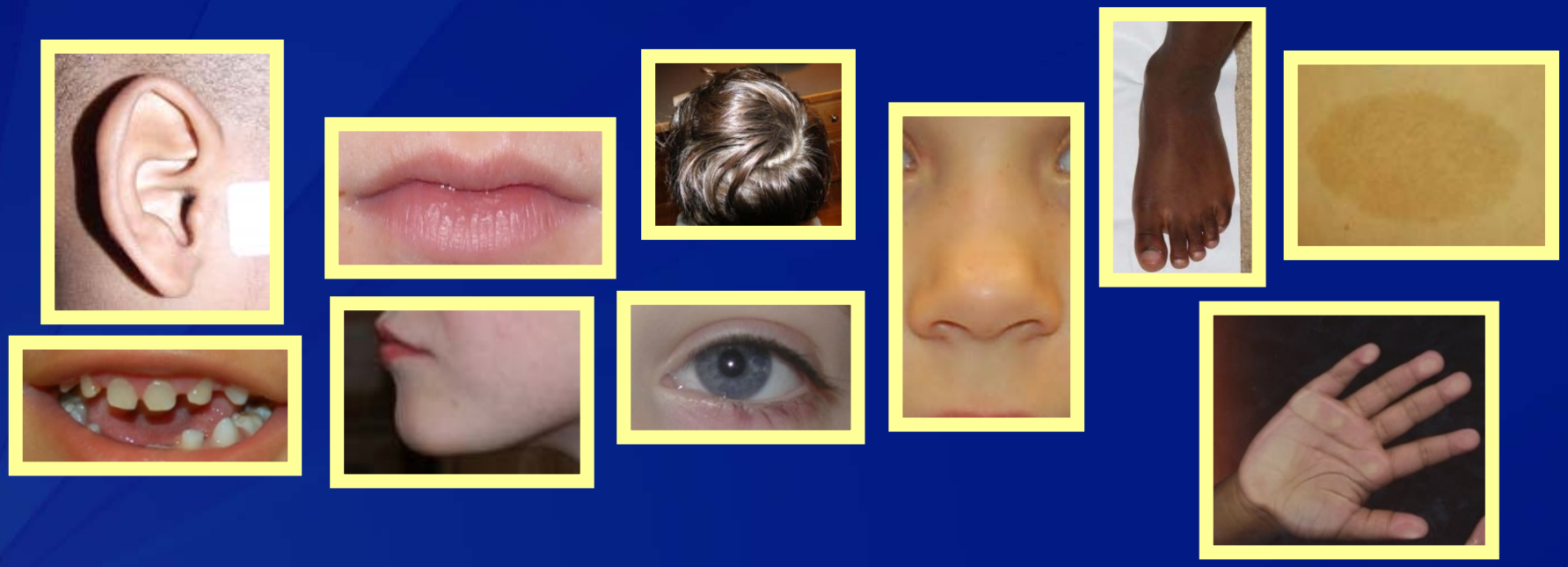
- **Clinic Visit--Exam and Dysmorphology Assessment**
  - Performed by study staff familiarized with dysmorphology
  - Measurement of child height, weight, and head circumference
  - Measurement of child foot length





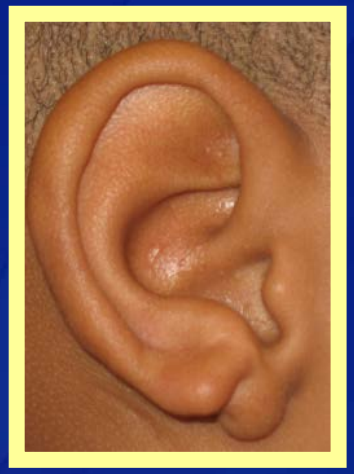
Data Collection

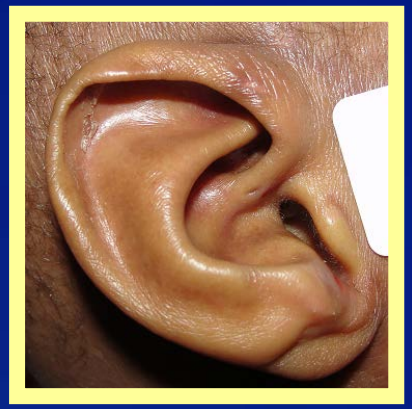
- **Clinic Visit--Exam and Dysmorphology Assessment**
  - Hand scans for measurements: Index finger length; Middle finger length; Ring finger length; Palm length; Total hand length
  - External exam for dysmorphic features: Head; Forehead; Hair; Face; Ears; Eyes; Eyebrows; Nose; Philtrum; Mouth; Lips; Teeth; Hands; Feet; Nails; Skin

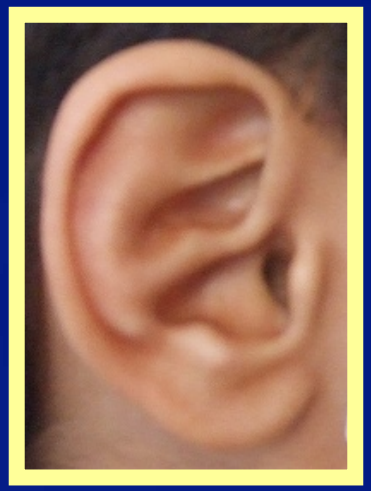


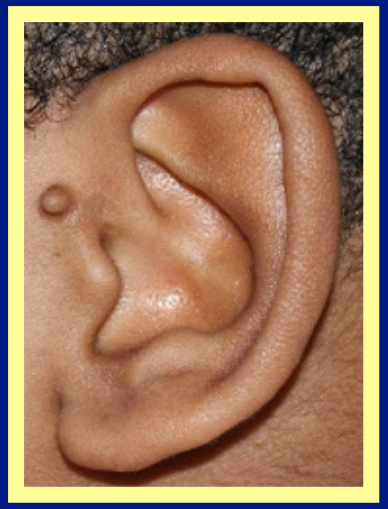
Data Collection

- **Clinic Visit--Exam and Dysmorphology Assessment**
  - Standardized photos of child
    - Obtain measurements: Interpupillary distance; Inner canthal distance; Palpebral fissure length; Philtrum length; Ear length
    - Document dysmorphic features









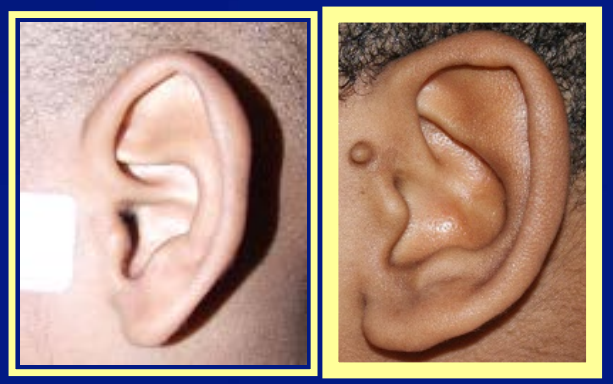
Dysmorphology Review

- Seven clinical geneticists were each assigned a body region for which they performed a standardized dysmorphology review on all children in the study

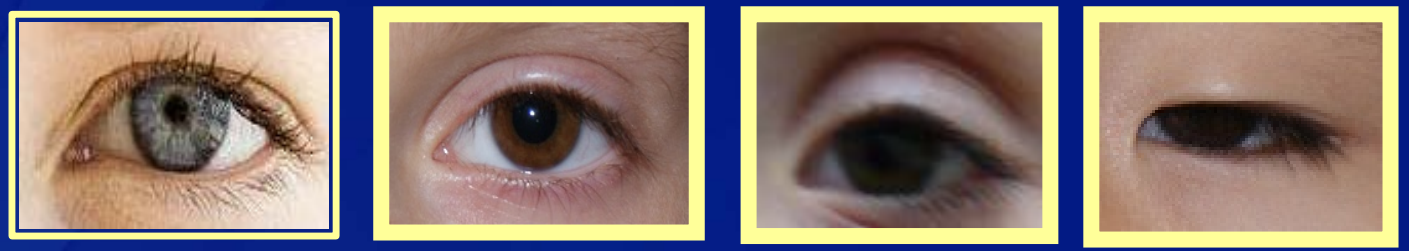
Geneticist	Body Region	# Features Reviewed
Art Aylsworth	Head, Hair, Face, & Neck	68
Ellen Elias	Hands & Feet	83
Julie Hoover-Fong	Growth & Skin	16
Stuart Shapira	Ears	90
Stuart Shapira	Mouth, Lips, & Teeth	26
Anne Tsai; Naomi Meeks	Nose & Philtrum	52
Elaine Zackai	Eyes & Eyebrows	62
	TOTAL	397

When is a Physical Feature Dysmorphic?

- **Occurs in ≤5% of the POP controls**
  - Absent vs. Present (e.g. Ear tag)
  - Spectrum in the Population (e.g. Ptosis) Statistical method applied to the POP group to categorize what part of the spectrum corresponds to “dysmorphic”



Absent Present



Absent Mild Moderate Severe

Dysmorphology Classification

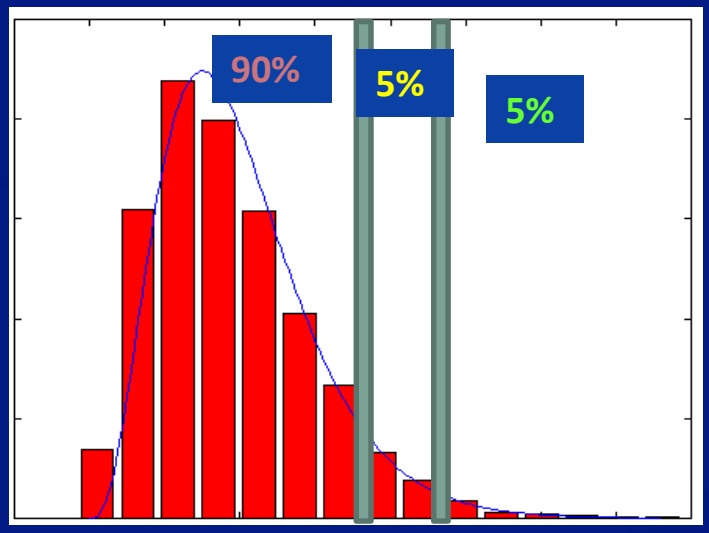
- The number of features considered dysmorphic for each child in POP were summed, Dysmorphology Scores were developed, and Scores fit to the log normal distribution

Dysmorphology Classification

≤90% = Non-dysmorphic

>90% and ≤95% = Equivocal

>95% = Dysmorphic



Study Population

Child Race/Ethnicity	POP	ASD	TOTAL
Non-Hispanic White	186	317	503
Non-Hispanic Black	98	119	217
Hispanic	91	90	181
TOTAL	375	526	901

- Dysmorphology reviews and classifications performed separately for each race/ethnicity

Final Dysmorphology Classification

POP			
	Non-dysmorphic	Equivocal	Dysmorphic
NHW	89.73%	7.03%	3.24%
NHB	89.58%	4.17%	6.25%
Hisp	90.00%	4.44%	5.56%

$\chi^2=2.72$; $p=0.606$

ASD			
NHB	Non-dysmorphic	Equivocal	Dysmorphic
NHW	69.03%	13.87%	17.10%
NHB	69.23%	13.68%	17.09%
Hisp	73.56%	9.20%	17.24%

$\chi^2=1.40$; $p=0.844$

Final Dysmorphology Classification

- Significant difference in the dysmorphology classification distributions between POP and ASD

Total	Non-dysmorphic	Equivocal	Dysmorphic
POP	89.76%	5.66%	4.58%
ASD	69.84%	13.04%	17.12%

$\chi^2=51.26$; $p<0.001$

- Partly attenuated by excluding those with known genetic syndromes

Total	Non-dysmorphic	Equivocal	Dysmorphic
POP	89.97%	5.57%	4.46%
ASD	72.52%	13.22%	14.26%

$\chi^2=39.59$; $p<0.001$

Summary

- This novel protocol defines a quantitative dysmorphology classification and identifies categories of Dysmorphic and Non-dysmorphic children with ASD in SEED
- This classification allows stratification of ASD phenotype for potentially more homogeneous assessment categories for studies of etiologic risk factors and genetic susceptibilities

Summary

- Future studies have been initiated that focus on identifying patterns of dysmorphic features that are predictive of various ASD phenotypes

Collaborators

- Aimee A. Alexander, CDC
- Arthur S. Aylsworth, UNC Medical School
- Ellen R. Elias, University of Colorado School of Medicine
- Julie E. Hoover-Fong, Johns Hopkins University
- Naomi J. L. Meeks, University of Colorado School of Medicine
- Laura A. Schieve, CDC
- Margaret C. Souders, Children's Hospital of Philadelphia
- Ann C. H. Tsai, University of Colorado School of Medicine
- Marshalyn H. Yeargin-Allsopp, CDC
- Elaine H. Zackai, Children's Hospital of Philadelphia

The participating families and the many staff and scientists from the SEED sites who contributed to the dysmorphology study

Highlights of the Findings of 5 SEED Studies

- **ASD Risk Factors Studies**

Autism Spectrum Disorder and Birth Spacing – Laura Schieve, PhD

Maternal Infection and Fever during Pregnancy and Risk of ASD– presented by M. Danielle Fallin, PhD on behalf of Lisa Croen, PhD

- **ASD Genetic Associations**

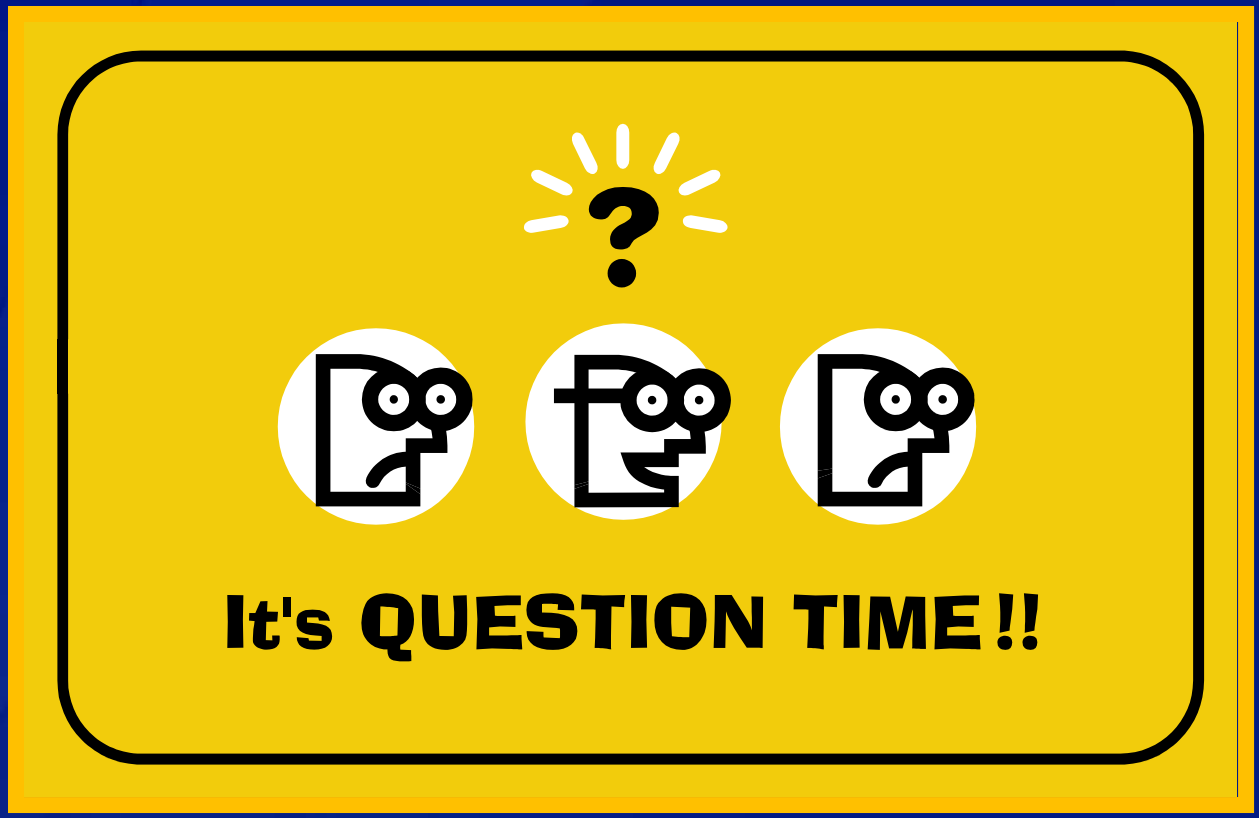
Peripheral Blood DNA Methylation and ASD – M. Danielle Fallin, PhD

- **ASD and Child Health Effects**

Gastrointestinal Symptoms in 2 – 5 Year Old Children – Ann Reynolds, MD

- **Characteristics of Children with ASD**

A Novel Protocol for Characterizing Dysmorphology to Enhance the Phenotypic Classification of ASD – Stuart Shapira, MD, PhD


It's QUESTION TIME!!

IACC
INTERAGENCY AUTISM
COORDINATING COMMITTEE

Break

Meeting of the IACC

Morning Agenda – continued

11:00 **Committee Business**

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

12:00 **Lunch**

These slides do not reflect decisions of the IACC and are for discussion purposes only.

IACC Committee Business

IACC Full Committee Meeting
October 24, 2017

Susan A. Daniels, Ph.D.
Director, Office of Autism Research Coordination
Executive Secretary, IACC
National Institute of Mental Health

Thanks to OARC Staff

Susan Daniels, Ph.D.
Director

Oni Celestin, Ph.D.
Science Policy Analyst

Karen Mowrer, Ph.D.
Science Policy Analyst

Jamie Kleiner
Science Policy Intern

Julianna Rava, M.P.H.
Science Policy Analyst

Rebecca Martin, M.P.H
Public Health Analyst

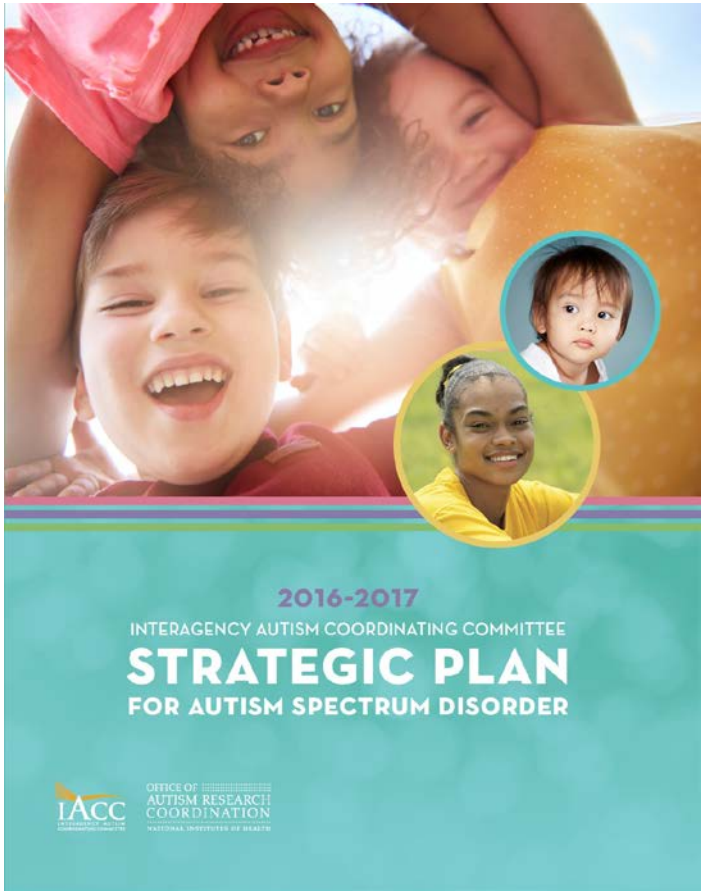
NEW! Matthew Vilnit, B.S.
Operations Coordinator

Angelice Mitrakas, **B.A.**
Management Analyst

Jeff Wiegand, **B.S.**
Web Development Manager

New publications available on IACC website

2016-2017 IACC Strategic Plan



- The IACC Strategic Plan (SP) provides a blueprint to guide autism-related efforts across federal agencies and partner private organizations.
- The IACC SP is organized around 7 community-based questions.
- The Plan includes 23 new objectives that address both research and services activities.

https://iacc.hhs.gov/publications/strategic-plan/2017/

2016-2017 IACC Strategic Plan – New Objectives

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

1. Strengthen the evidence base for the benefits of early detection of ASD.
2. Reduce disparities in early detection and access to services.
3. Improve/validate existing, or develop new tools, methods, and service delivery models for detecting ASD in order to facilitate timely linkage of individuals with ASD to early, targeted interventions and supports.

CROSS-CUTTING

1. Support research to understand the underlying biology of sex differences in ASD, possible factors that may be contributing to underdiagnoses, unique challenges that may be faced by girls/women on the autism spectrum, and develop strategies for meeting the needs of this population.

QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

1. Foster research to better understand the processes of early development, molecular, and neurodevelopmental mechanisms, and brain circuitry that contribute to the structural and functional basis of ASD.
2. Support research to understand the underlying biology of co-occurring conditions in ASD and to understand the relationship of these conditions to ASD.
3. Support large scale longitudinal studies that can answer questions about the development of ASD from pregnancy through adulthood and the natural history of ASD across the lifespan.

2016-2017 IACC Strategic Plan – New Objectives

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

1. Strengthen understanding of genetic risk and resilience factors for ASD across the full diversity and heterogeneity of those with ASD, enabling development of strategies for reducing disability and co-occurring conditions of ASD.
2. Understand the effects on ASD and resilience of individual and multiple exposures in early development, enabling development of strategies for reducing disability and co-occurring conditions in ASD.
3. Expand knowledge about how multiple environmental and genetic risk and resilience factors interact through specific biological mechanisms to manifest in ASD phenotypes.

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

1. Develop and improve pharmacological and medical interventions to address both core symptoms and co-occurring conditions in ASD.
2. Create and improve psychosocial, developmental, and naturalistic interventions for the core symptoms and co-occurring conditions in ASD.
3. Maximize the potential for technologies and development of technology-based interventions to improve the lives of people on the autism spectrum.

2016-2017 IACC Strategic Plan – New Objectives

QUESTION 5: WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

1. Scale up and implement evidence-based interventions in community settings.
2. Reduce disparities in access and in outcomes for underserved populations.
3. Improve service models to ensure consistency of care across many domains with the goal of maximizing outcomes and improving the value that individuals get from services.

QUESTIONS 6: HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

1. Support development and coordination of integrated services to help youth make a successful transition to adulthood and provide supports throughout the lifespan.
2. Support research and implement approaches to reduce disabling co-occurring physical and mental health conditions in adults with ASD with the goal of improving safety, reducing premature mortality, and enhancing quality of life.
3. Support research, services activities, and outreach efforts that facilitate and incorporate acceptance, accommodation, inclusion, independence, and integration of people on the autism spectrum into society.

2016-2017 IACC Strategic Plan – New Objectives

QUESTIONS 6: HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

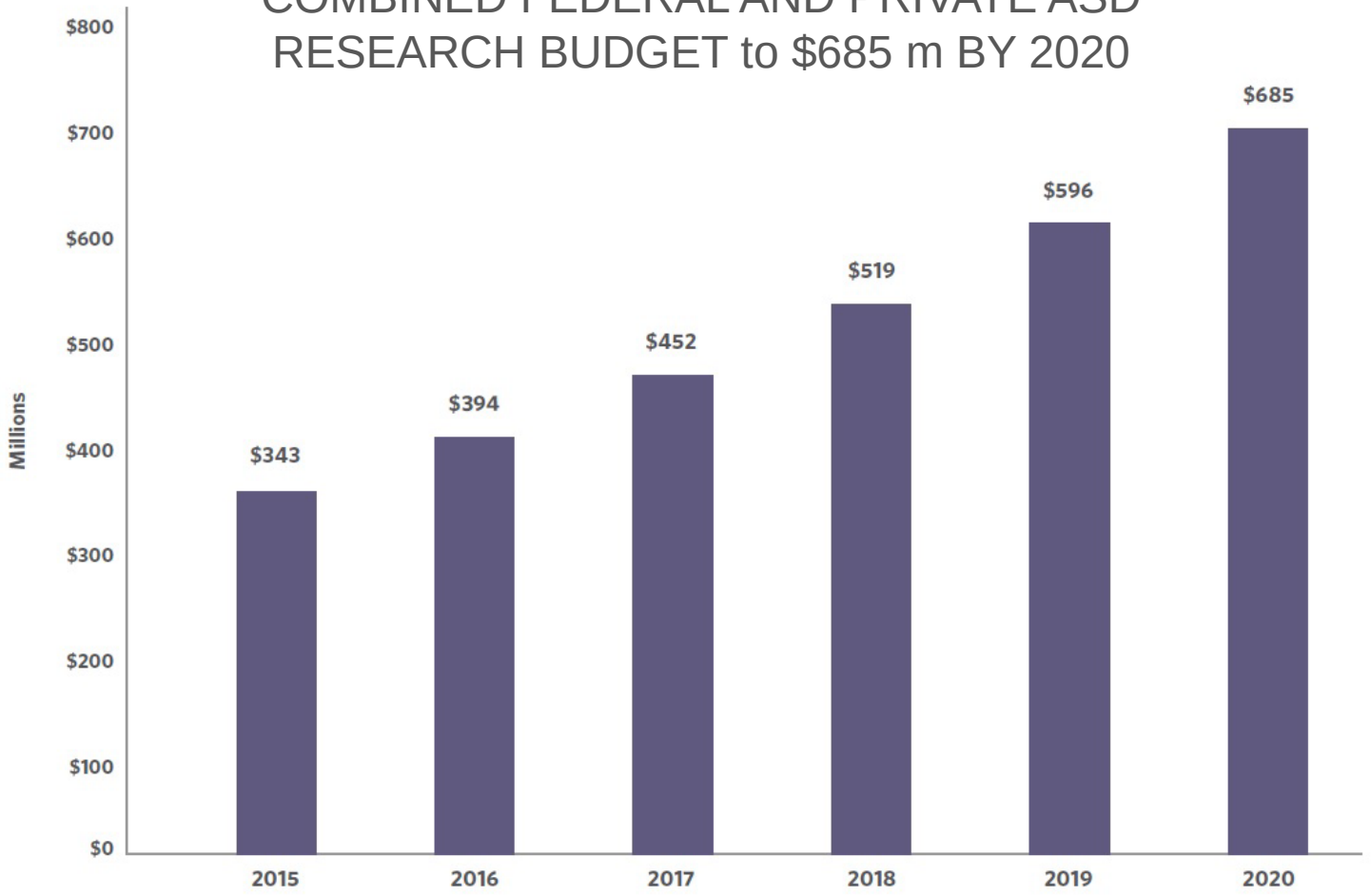
1. Support development and coordination of integrated services to help youth make a successful transition to adulthood and provide supports throughout the lifespan.
2. Support research and implement approaches to reduce disabling co-occurring physical and mental health conditions in adults with ASD with the goal of improving safety, reducing premature mortality, and enhancing quality of life.
3. Support research, services activities, and outreach efforts that facilitate and incorporate acceptance, accommodation, inclusion, independence, and integration of people on the autism spectrum into society.

QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

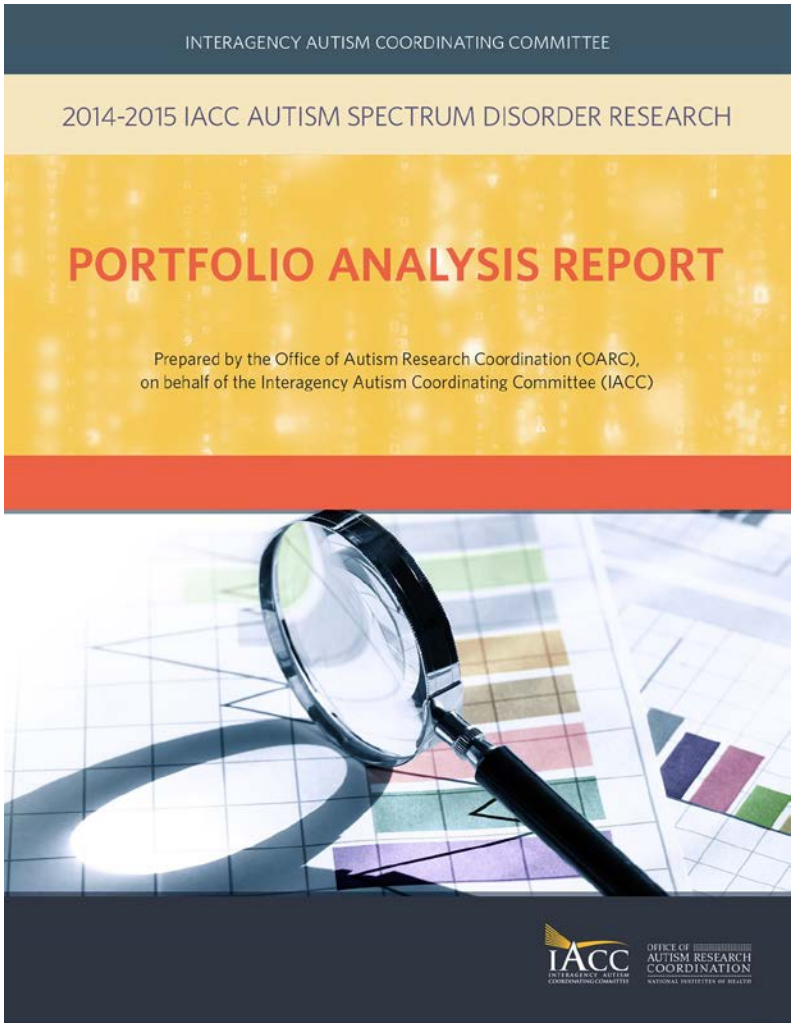
1. Promote growth, integration, and coordination of biorepository infrastructure.
2. Develop, enhance, and link data repositories.
3. Strengthen ASD surveillance systems to further understanding of the population of individuals with ASD, while allowing comparisons and linkages across systems as much as possible.

2016-2017 IACC Strategic Plan – Budget Recommendation

THE IACC RECOMMENDS DOUBLING THE COMBINED FEDERAL AND PRIVATE ASD RESEARCH BUDGET to $685 m BY 2020



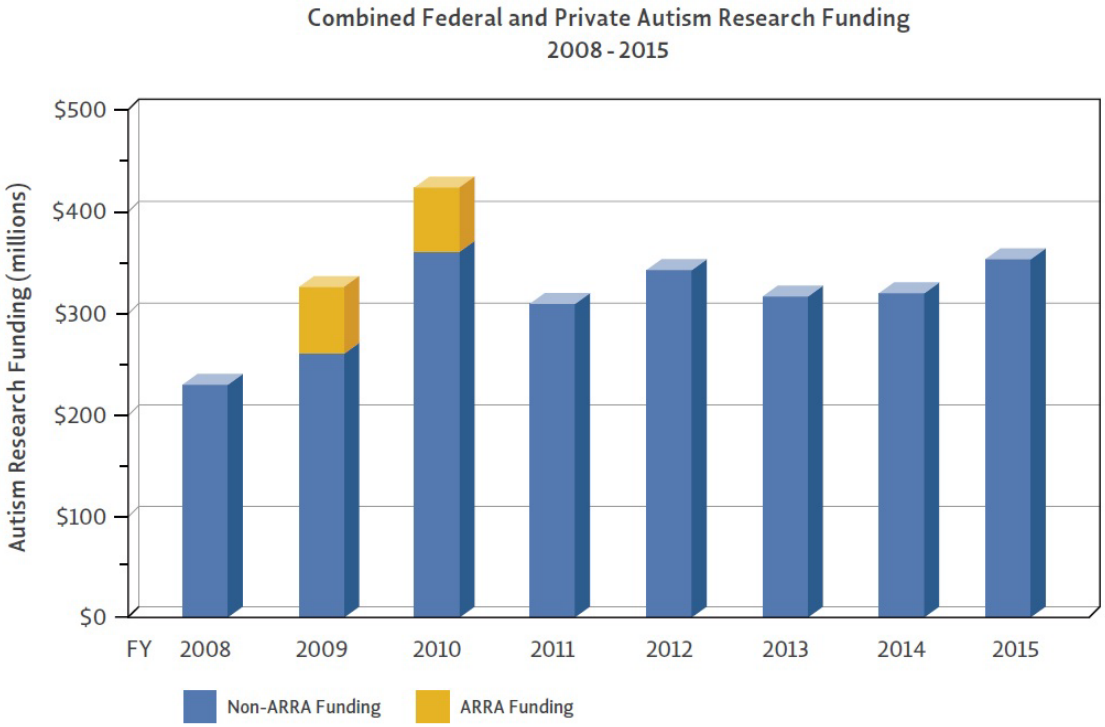
2014-2015 IACC Portfolio Analysis Report



- The *2014-2015 IACC ASD Research Portfolio Analysis Report* represents the eighth year of data collected and the sixth comprehensive report of U.S. ASD research funding across both the Federal and private sectors.
- It is the last analysis that measure research progress by the objectives from the *2011 IACC Strategic Plan*.
- 2014 and 2015 ASD portfolio data are now available through the IACC/OARC Autism Research Database

https://iacc.hhs.gov/portfolio-analysis/2015/index.shtml

2014-2015 IACC Portfolio Analysis Report



- Overall funding for ASD research totaled $309.9 million and spanned 1,441 projects in 2014 and reached $342.6 million covering 1,410 projects in 2015.
- Over the eight years, autism research showed a general upward trend in funding, increasing by 35% since 2008.

2014-2015 IACC Portfolio Analysis Report

Summary of Overall Progress on Strategic Plan Objectives through 2015

Inactive (Red) Objectives

Complete (Green) or Partially Complete (Yellow) Objectives

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Total	Percentage
Number of Complete Objectives	6	7	11	6	4	1	10	45	57.7%
Number of Partially Complete Objectives	3	2	4	6	5	7	4	31	39.7%
Number of Inactive Objectives	0	0	0	0	0	0	2	2	2.6%
Total	9	9	15	12	9	8	16	78	100%

In 2015, significant progress was made toward completing the objectives in the *2011 Strategic Plan*, with 97% (76 objectives) of the 78 objectives either partially or fully completed.

New IACC Working Groups

- In 2016 the IACC agreed to convene 3 working groups on issues of critical importance to the autism community, with work to begin following completion of the 2016-2017 IACC Strategic Plan

Topics:

- Health and Wellness
- Safety
- Housing

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Health and Wellness Working Group

- Title: Improving Health Outcomes for Individuals on the Autism Spectrum
- Scope:
  - Health and general wellness
  - Co-occurring conditions and preventative approaches to address them, e.g. obesity
  - Co-occurring mental health conditions
  - Premature mortality
  - Medical practitioner training (i.e. increasing understanding of autism among physicians, supporting community doctors who provide medical care for adults with autism)
  - Parental Mental Health

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Safety Working Group

Scope:

- Wandering
- Self-injurious behavior (or this could be part of co-occurring conditions)
- Seclusion and restraint
- Interactions with law enforcement

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Housing Working Group

Scope:

- Research and best practices on housing
- Implementation of current federal regulations
- Housing issues faced by those with ASD with more severe disabilities

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Working Groups: Next Steps

Questions:

- What products does the IACC want the working groups to develop as an outcome?
- What structure, activities, and timing will be most efficient to develop these products and allow the Committee to complete their work on these topics by September 2019?
- Can the products of the working groups be helpful toward meeting IACC requirements (i.e., producing an annual update of the Strategic Plan)?

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Recent Event – Autism in Girls and Women seminar

- A panel discussion of issues concerning autism in girls and women
- Co-sponsored by OARC and NIMH Office of Research on Disparities and Global Mental Health (ORDGMH)
- Link to archived webcast available on IACC website: https://iacc.hhs.gov/meetings/autism-events/2017/september19/autism-in-girls.shtml

IACC
INTERAGENCY AUTISM
COORDINATING COMMITTEE

Lunch

Meeting of the IACC

Afternoon Agenda

1:00 **Public Comment Session**

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

Karen Mowrer, Ph.D.
Science Policy Analyst, NIMH

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Meeting of the IACC

Afternoon Agenda

2:15 **Autism and Suicide**

Sarah Cassidy, M.Sc., Ph.D.
Assistant Professor
University of Nottingham, United Kingdom

Lisa Horowitz, Ph.D., M.P.H.
Staff Scientist and Clinical Psychologist
National Institute of Mental Health

Colleen Carr, M.P.H.
Deputy Director
National Action Alliance for Suicide Prevention

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Meeting of the IACC

Afternoon Agenda

3:30 **Committee Discussion**

4:00 **Afternoon Break**

4:15 **Summary of Advances Discussion**

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

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Meeting of the IACC

Afternoon Agenda

4:00 **Round Robin**

5:00 **Closing Remarks and Adjournment**

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Meeting of the IACC

Public Comments Session

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Meeting of the IACC

Public Comments Session

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Autism and Suicide

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University of Nottingham
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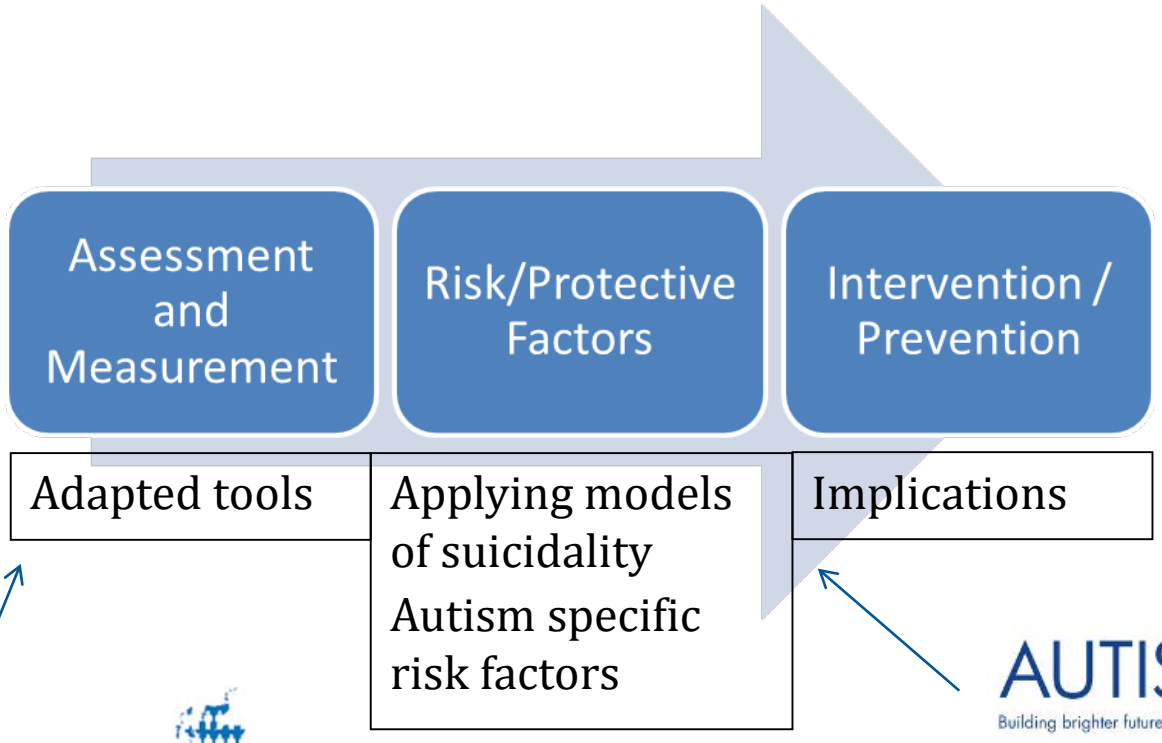
E·S·R·C ECONOMIC & SOCIAL RESEARCH COUNCIL

Suicidality in Autism

Dr. Sarah Cassidy
@MHAutism

Who we are

- **Mental Health Autism (MHAutism)**
  - Understanding and reducing mental health problems and suicide in autism



AUTISTICA
Building brighter futures through autism research

E·S·R·C ECONOMIC & SOCIAL RESEARCH COUNCIL

MHAutism

Collaboration for leadership in applied health research and care
East of England

NHS
National Institute for Health Research

Language

- **Recent research showed that the autism community use a range of terms to describe themselves:**
  - Autistic
  - Aspie
  - On the spectrum
  - Person with autism

- **On the whole, ‘autistic person’ was most preferred by the autism community, and ‘person with autism’ was preferred by professionals**

Mental Health in Autism

- **Majority of autistic adults (79%) meet criteria for at least 1 mental health condition (Lever and Guerts, 2016)**

- **A significant risk factor for suicide in the general population (Kasper et al. 1996; Baraclough et al. 1974)**

<u>What about suicide in autism?</u>

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Suicidality in Autism

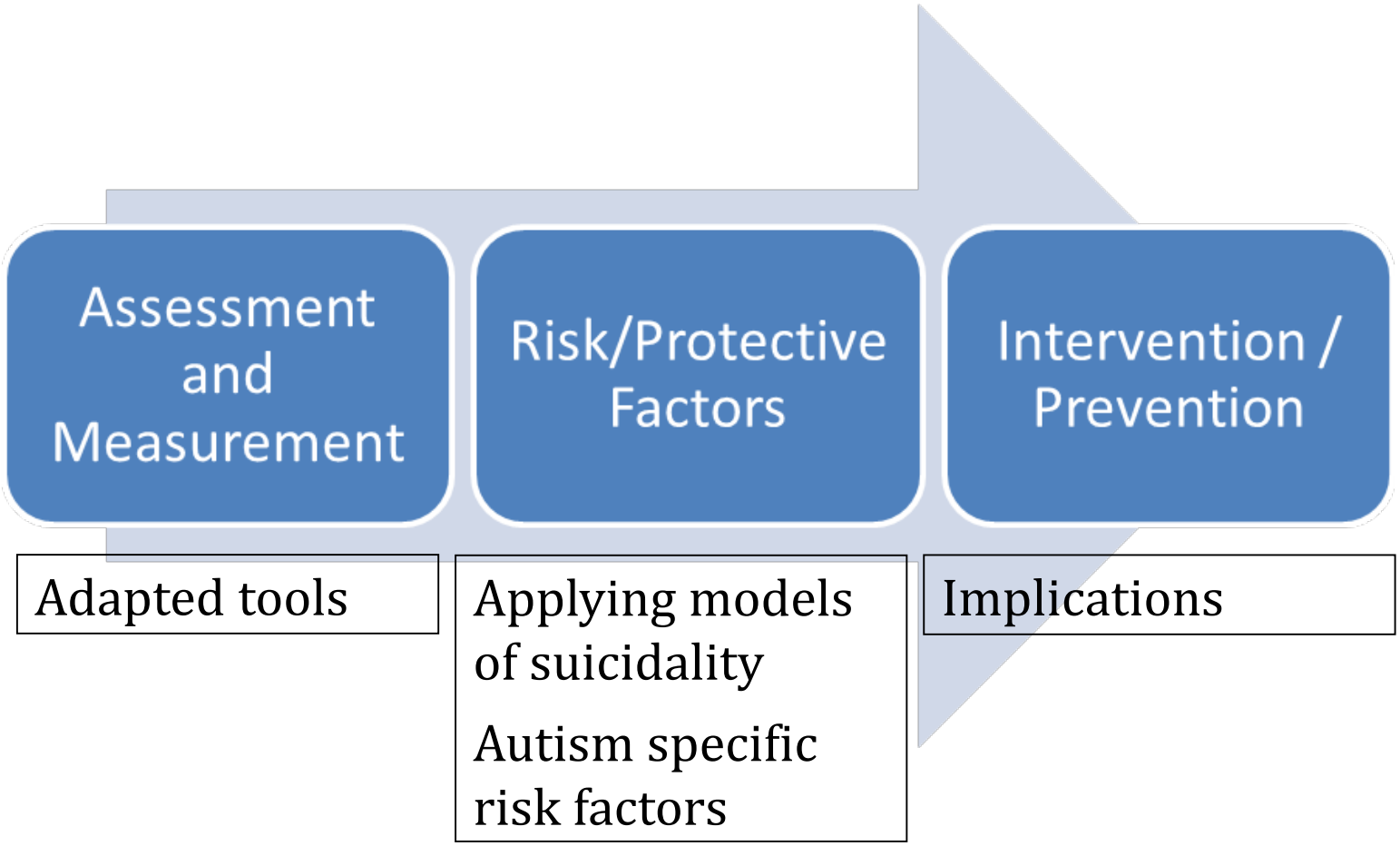
- **374 newly diagnosed adults with Asperger Syndrome; suicidal ideation 66%; suicide plans/attempts 35%, depression 31%**
  - Autistic traits and depression risk factors for suicidality (Cassidy et al. 2014)

- **Autistic adults significantly more likely to die by suicide than the general population**
  - Being female, autism without LD, and depression are risk factors (Hirvikoski et al. 2015)

Growing number of ‘counting’ studies

Not enough about *Why*

Overview


Assessment and Measurement
Risk/Protective Factors
Intervention / Prevention
Adapted tools
Applying models of suicidality
Autism specific risk factors
Implications

Assessment and Measurement

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Challenge of Measurement in Autism

- **Alexythymia:** under/over reporting of suicidality?
- **Theory of Mind, literal interpretation:** over reporting of suicidal feelings?
- **Overlapping behaviours?** E.g. social withdrawal, sleep problems …
- **Unique aspects of suicidality in Autism:** Reduced cognitive flexibility …

Involve autism community in development of Qs …

Adapting Tools

- **Stage 1: Systematic review of measurement tools to assess suicidality in adults with/without autism diagnosis**
- **Stage 2: Focus groups, cognitive interviews and survey to inform and test adaptions**
- **Stage 3: Explore measurement properties of adapted tools**
- **Stage 4: Establish prevalence of suicidality in autistic adults in the UK**

Adaptation: Stage 1 - 2

- **No validated suicidality assessment tools used in autism, or validated for this group**
- **Suicide Behaviours Questionnaire Revised (SBQ-R) brief 4-item candidate tool selected**
- **Four focus groups with variety of stakeholders (autistic adults, service providers, clinicians)**
  - How clear are the questions, how important are the questions, are any important questions missing?
- **2 x 15 cognitive interviews with autistic adults**
  - Tell me what you are reading and thinking about as you work through the questionnaire
- **Next step – online survey to feedback on candidate tool**

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Adaption Stage 2

- **Difficulties with language -** break up questions, fewer options
- **Difficulties with memory and time –** diary/calendar?
- **Literal interpretation** – exactly how many thoughts, accidentally overdosing without intent to end life, “What is a plan … you always have a plan …”
- **Insensitive language** – “commit suicide”, “kill yourself”
- **Purpose of the assessment** – “Why are these cells blue?”
- **Rapport and trust** – “What will happen to me?”

Risk / Protective Factors

Mental Health in Autism

- **Study 1: Exploration of autistic traits and the Interpersonal Psychological Theory**
- **Study 2: Co-designed suicidality survey with the autism community**
- **Study 3: Preliminary findings from first Psychological Autopsy study of suicide in autism**

Interpersonal Psychological Theory of Suicide (IPTS)

Desire to die

Thwarted Belongingness
(I am alone)

Perceived Burdensomeness
(I am a burden)

- Social difficulties
- Social exclusion
- Unemployment

Autistic Traits

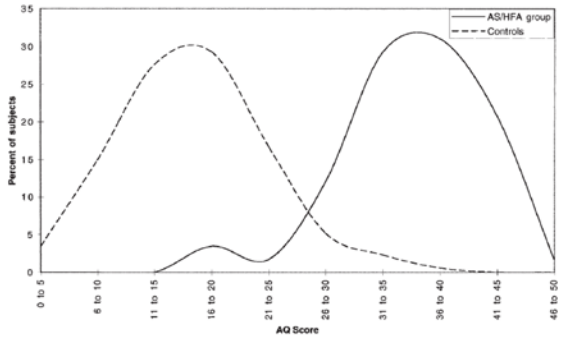

Fig. 1. AQ scores in AS/HFA group and controls (Groups 1 and 2).

Pelton and Cassidy (2017). Are autistic traits associated with suicidality? A test of the Interpersonal-Psychological Theory of Suicide in a non-clinical young adult sample. Autism Research.

Joiner, T. E. (2005). Why people die by suicide. Cambridge, MA: Harvard University Press.

Results

- **163 general population young adults (18-30 years)**

- **Autistic traits significantly predicted Perceived Burdensomeness and Thwarted Belongingness (controlling for age, gender and depression)**

Autistic traits associated with risk of suicidality through thwarted belonging and perceived burdensomeness

Participatory Research

- **Models and measures developed for the general population**
- **So we formed a steering group of 8 autistic adults who had experienced mental health difficulties and/or suicidality:**
  - Identify themes which may increase or decrease risk of experiencing mental health problems and/or suicidality
  - Develop a survey to capture these areas

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Themes identified from the focus groups

- Isolation – social and non-social
- Lack of belonging in an autism unfriendly world – thoughts of ‘leaving’
  - Lack of opportunities – employment, education etc.
- Social and communication difficulties, and tendency to mask these – mental health problems, difficulties accessing help
- Lack of autism friendly services
- Late diagnosis, misdiagnosis, diagnostic overshadowing
  - Lack of post diagnostic support
- Not supporting autistic people to have a positive identity – strengths as well as weaknesses – lack of resilience

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Results

- 168 autistic adults (67 male, 101 female), and 108 control females, aged 20-60 years old
- Autism group mean SBQ-R (10.31) significantly higher than the recommended cut off for psychiatric populations (>=8); 69.8% at or above this cut off
- Significantly higher SBQ-R in autistic than control females (10.61 vs 6.27) (controlling for age, education, occupational status, living arrangements, co-morbid developmental and mental health conditions)
- Autism group - history of NSSI, at least one mental health condition, unemployment, and camouflaging associated with significantly higher SBQ-R

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Psychological Autopsy

- **Preliminary results from first stage of a Psychological Autopsy study aiming to:**
  - establish whether definite/possible autism diagnoses are over-represented amongst people who died by suicide in the UK
  - compare the characteristics of those with and without autism who have died by suicide in the UK
- **Involve analysis of coroners inquests and interviews with friends and family of the person who died**
- **Results could identify targets to prevent suicide in autism**

Psychological Autopsy

- **Coroners records for the period 2014-2015 recording a suicide, open, drug/alcohol or narrative conclusion were analysed for:**
  - Evidence of autism (diagnosed and un-diagnosed)
  - Inter-rater reliability was >80% for evidence of autism

Evidence of autism?	Definition
Definite Diagnosis	Clinical diagnosis of autism noted in the inquest.
Strong Evidence	Possible diagnosis noted, *and* clear indicators in >=2 areas: 1) Social/Communication difficulties; 2) Narrow interests; 3) Routines; 4) Sensory difficulties; 5) Special educational needs in childhood.
Possible Diagnosis	Clear indicators in >=2 areas (as above), but not noted in record.
No Evidence	No clear indicators of autism in record.

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Results

- 219 coroners inquest records were assessed, 150 which were ruled a likely suicide according to ICD-10 criteria.
- 11% had evidence of autism, significantly higher than the general population rate (1%)

Evidence of Autism?	Likely Suicide			Self harm / vulnerability		
	Suicide N (%)	% Male	Mean age	Self-harm N (%)	% Male	Mean age
No Evidence	133 (88.7)	80.4	46.8	39 (90.7)	82	45.5
Possible Diagnosis	14 (9.3)	71.4	47.23	**4 (9.3)**	75	36.2
Strong Evidence	2 (1.3)	100	33.5	0	0	-
Definite Diagnosis	1 (0.7)	100	20	0	0	-
Evidence of Autism	**17 (11.3)**	76.5	44.1	4 (9.3)	75	36.2
Total	150 (100)	80	46.5	43 (100)		

Implications for Intervention / Prevention

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Overall Summary

- **Suicidality in autism significantly higher than psychiatric groups**
  - However, unclear whether this is under/over-estimated
- **Late diagnosed / undiagnosed adults without ID appear most at risk**
- **Increased vulnerability to risk factors for suicidality:**
  - Reduced sense of belonging, isolation
  - Difficulty accessing support and treatment
  - Unemployment, co-morbid mental health conditions
- **Suicidality in autism beyond co-morbidities:**
  - One new potential autism specific risk factor - camouflaging

Implications

- **Timely diagnosis of autism, and post diagnostic support.**
- **Identifying and supporting ‘the lost generation’ of autistic adults.**
- **Promoting inclusion, independence and autonomy of autistic people:**
  - access to education and employment, positive identity and esteem, resilience – sense of belonging.

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Thanks to …

Mental Health Autism: Dr. Louise Bradley, Dr. Rebecca Shaw.

Newcastle University: Dr. Jacqui Rodgers, Dr. Sarah Wigham, Dr. Jeremy Parr.

ARC and CLASS clinic: Prof. Simon Baron-Cohen, Dr. Carrie Allison, Dr. Paul Bradley, Dr. Janine Robinson, Meghan McHugh, Dr. Gareth Richards, Dr. Rebecca Kenny.

Sarah.Cassidy@Nottingham.ac.uk
@MHAutism
MHAutism.coventry.ac.uk

Screening for Suicide Risk in Youth with Autism Spectrum Disorder and other Neurodevelopmental Disorders

Lisa M. Horowitz, PhD, MPH
Audrey Thurm, PhD

Office of the Clinical Director
National Institute of Mental Health
Intramural Research Program

Interagency Autism Coordinating Committee Meeting
October 24, 2017

NIH National Institute of Mental Health

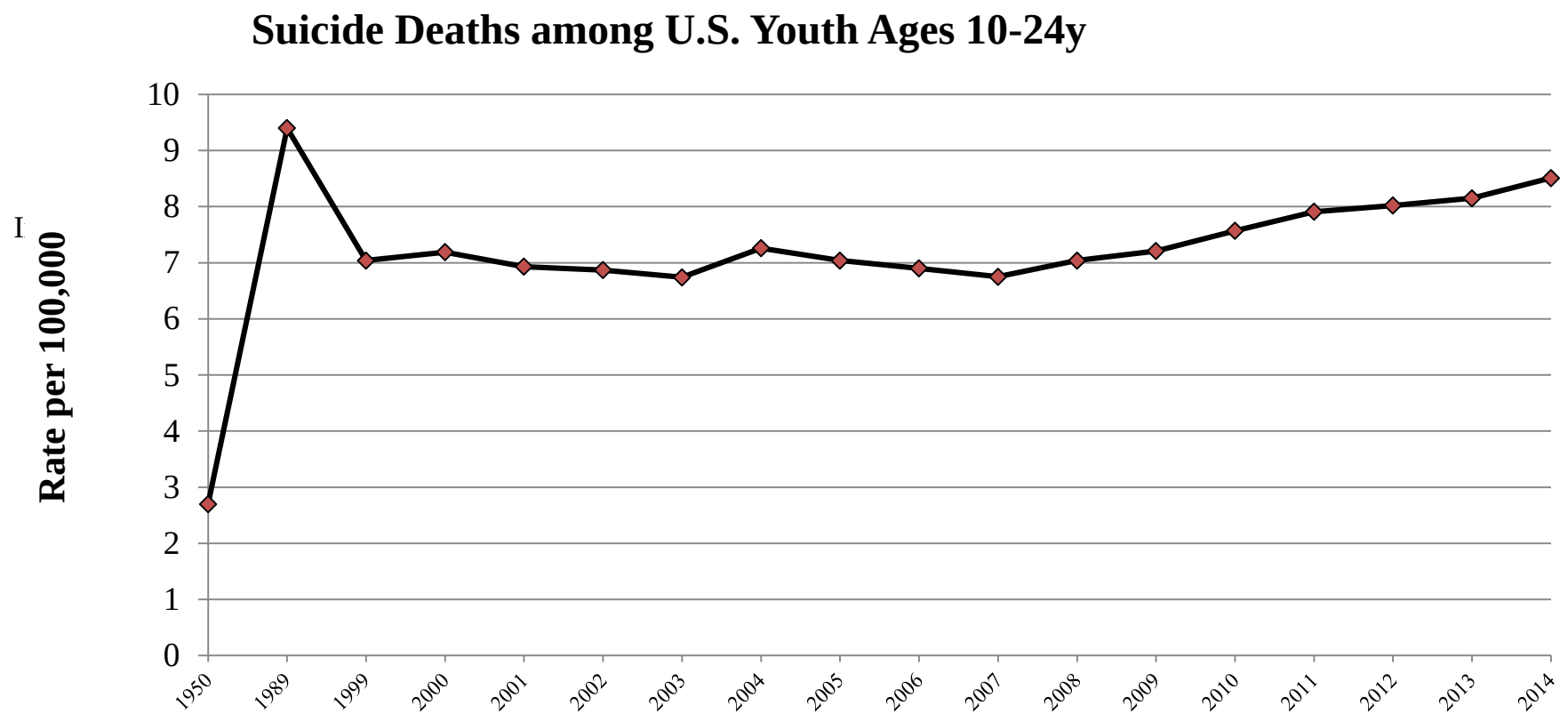
The views expressed in this presentation do not necessarily represent the views of the NIH, DHHS, or any other government agency or official. We have no financial conflicts to disclose.

Overall Objectives

- Brief epidemiology of youth suicide
- Unique challenges in screening the ASD population
  - And related populations, like ID
- Suicide risk screening tool instrument development overview
- Clinicians require population-specific and site-specific validated screening instruments

Youth Suicide in the U.S.

- **2nd leading cause of death** for youth aged 10-24y
- 5,904 suicide deaths in 2015



CDC WISQARS, 2016

Suicidal Behavior and Ideation

Suicidal Behavior

- **~2 million adolescents** attempt suicide annually
  - 9% of high school students attempted suicide one or more times in the past year

Suicidal Thoughts

- 18% of high school students reported “seriously considered attempting suicide” in the last year

Youth Risk Behavior Surveillance, 2015

Younger Children and Suicidality

- Children under 12 yrs plan, attempt and die by suicide
  - 2nd leading cause of death for 10-14 year olds
  - 10th leading cause of death for children ages 5-11 years

CDC, 2015; CDC, 2016; Tishler, Reiss, & Rhodes, 2007; Natl Vital Stat Rep, 2006

Suicide in ASD populations

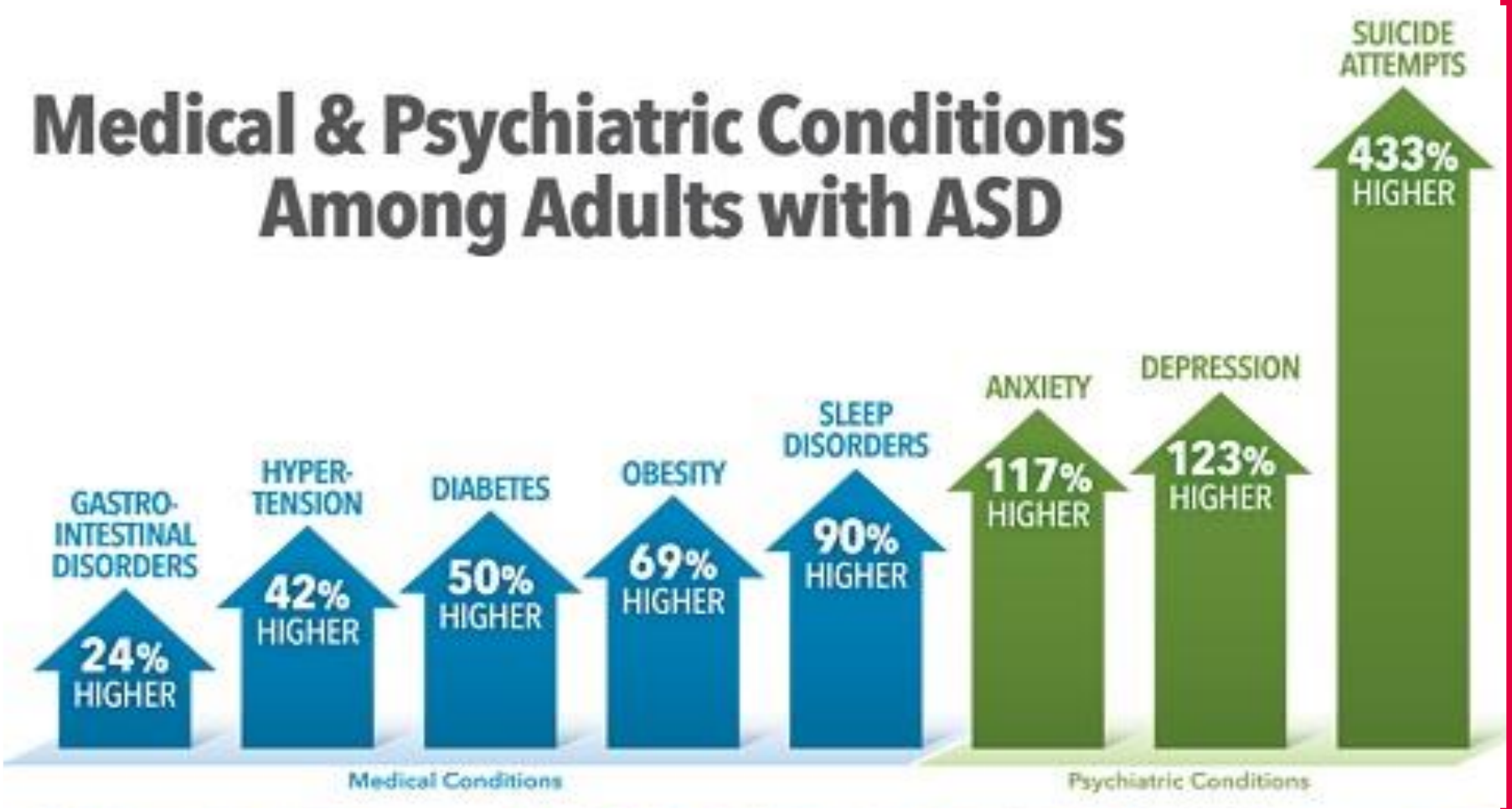


Image courtesy Lisa Croen, Kaiser Permanente Division of Research

Mayes, 2013; Richa, 2014

High Risk Factors

- **Previous attempt**
- **Medical illness**
- Mental illness
- Symptoms of depression, anxiety, agitation, impulsivity
- Exposure to suicide of a relative, friend or peer
- Physical/sexual abuse history
- Drug or alcohol abuse
- Lack of mental health treatment
- Suicide ideation
- Over age 60 and male
- Between the ages of 15 and 24
- **Isolation**
- Hopelessness

High Risk Factors for ASD population

- Higher IQ
  - IQ scores higher in suicidal youth than non-suicidal youth
  - Young people with ASD without comorbid ID at higher risk
  - Findings inconclusive
- Comorbid Axis I disorders
  - Psychiatric disorders correlated with elevated suicidal ideation and behavior.
  - 67% of adolescents with ID and/or ASD who expressed suicidal ideation met criteria for mood disorder
- Recent psychosocial stressors for those with suicidal ideation
  - 37% experienced loss in family
  - Less family and social support
  - Greater rejection, stress, and isolation
  - Difficulties with perspective taking

Ludi et al. 2012, Carlson et al, 1994; Walters 1995; Harris 2006; Coulter 1980

Can we save lives by screening for suicide risk?
Experience from the medical setting

Underdetection

- Majority of those who die by suicide have contact with a medical professional within 3 months of killing themselves
  - 80% of adolescents contact within 3 months
  - Frequently present with somatic complaints

- **ASD population**: suicidal behavior may be overlooked due to diagnostic overshadowing and communication difficulties

Blum, 1996; Clark, 1993; Frankenfield, 2000; Gairin, 2003; Hannon & Taylor, 2013; Pan, 2009; Rhodes 2013

What are valid questions that nurses/physicians can use to screen pediatric patients for suicide risk?

Screening vs. Assessment: What's the difference?

- **Suicide Screening**
  - Identify individuals at risk for suicide
  - Oral, paper/pencil, computer
- **Suicide Assessment**
  - Comprehensive evaluation
  - Confirms risk
  - Estimates imminent risk of danger to patient
  - Guides next steps

Ask Suicide-Screening Questions (ASQ)

- 3 pediatric EDs
  - Children's National Medical Center, Washington, DC
  - Children's Hospital Boston, Boston, MA
  - Nationwide Children's Hospital, Columbus, OH

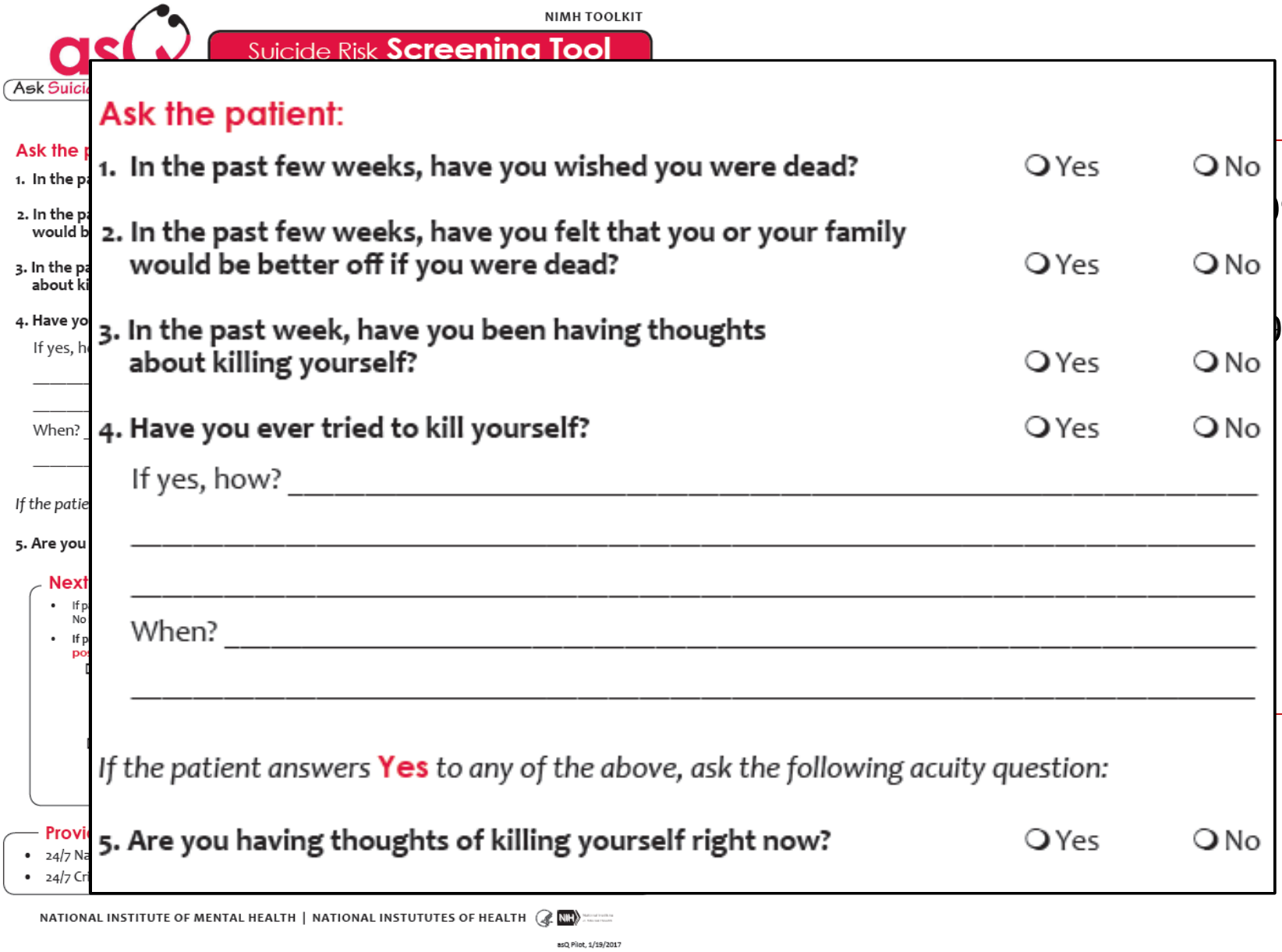
- September 2008 to January 2011

- 524 pediatric ED patients
  - 344 medical/surgical, 180 psychiatric
  - 57% female, 50% white, 53% privately insured
  - 10 to 21 years (mean=15.2 years; SD = 2.6y)

Horowitz et al. (2012) *Arch Pediatr Adolsc Med*

ASQ Study (con't)

- Administered 17 candidate items:
  - "Have you ever felt hopeless, like things would never get better?"
  - "Do you feel like you might as well give up because you can't make things better for yourself?"
- Administered gold standard: Suicidal Ideation Questionnaire (SIQ; Reynolds, 1987)
- Examined the least number of items with sound psychometrics
- Positive responses received psychiatric consultation



NIMH TOOLKIT

Suicide Risk Screening Tool

Ask the patient:

1. **In the past few weeks, have you wished you were dead?** ❍ Yes ❍ No
2. **In the past few weeks, have you felt that you or your family would be better off if you were dead?** ❍ Yes ❍ No
3. **In the past week, have you been having thoughts about killing yourself?** ❍ Yes ❍ No
4. **Have you ever tried to kill yourself?** ❍ Yes ❍ No

   If yes, how? _____

   _____

   _____

   When? _____

   _____

If the patient answers **Yes** *to any of the above, ask the following acuity question:*

5. **Are you having thoughts of killing yourself right now?** ❍ Yes ❍ No

NATIONAL INSTITUTE OF MENTAL HEALTH | NATIONAL INSTUTUTES OF HEALTH

asQ Pilot, 1/19/2017

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National Institute of Mental Health

Horowitz, Bridge, Teach, Ballard…Pao, et al. (2012) *Arch Pediatr Adolsc Med*

Results

- 98/524 (18.7%) screened positive for suicide risk
  - 14/344 (4%) medical/surgical chief complaints
  - 84/180 (47%) psychiatric chief complaints
- Feasible
  - 20 seconds
  - Non-disruptive to workflow
- Acceptable
  - Parents/guardians gave permission for screening
  - Over 95% of patients were in favor of screening
- ASQ is now available in the public domain
  - Translated into 8 languages

Horowitz et al. (2012) *Arch Pediatr Adolsc Med*

“What about screening kids with ASD?”

-Dr. Rachel Greenbaum

NIH National Institute of Mental Health

Literature Search Conclusion

- Patients presenting with suicidal thoughts present a high anxiety situation for clinicians
  - ASD patients present different challenges for clinicians
- Youth with ID and ASD have been excluded from research studies
- **There are currently no standardized tools developed to screen for suicide risk in youth with ASD**

Suicide Risk in People with ID

Review Article

Suicide Risk in Youth with Intellectual Disabilities: The Challenges of Screening

Erica Ludi, BS,* Elizabeth D. Ballard, MA,† Rachel Greenbaum, PhD,‡ Maryland Pao, MD,* Jeffrey Bridge, PhD,§ William Reynolds, PhD,‖ Lisa Horowitz, PhD, MPH*

ABSTRACT: Children and adolescents with intellectual disabilities (IDs), often diagnosed with comorbid psychiatric disorders, are a vulnerable population who may be at risk for developing suicidal thoughts and behaviors. Previous research has demonstrated that direct suicide screening can rapidly and effectively detect suicide risk and facilitate further clinical evaluation and management. Currently, there are no measures that screen for suicide risk designed specifically for individuals with ID. A review of the literature was conducted to (1) estimate the prevalence of suicidal thoughts, behaviors, and deaths by suicide in children and adolescents with ID; (2) describe associations between youth with ID and suicide risk; and (3) identify the limitations of commonly used suicide screening measures developed for non-ID youth. The literature review confirms that suicide risk exists in this population; youth with ID think about, attempt, and die by suicide. Standardized suicide risk screening is challenged by the lack of measures developed for this population. A summary of the findings is followed by a discussion of the practical clinical considerations surrounding the assessment of suicide risk in youth with ID.

*(J Dev Behav Pediatr 33:*431–440, 2012) **Index terms:** youth suicide, intellectual disability, developmental delay, suicide screening, assessment.

Ludi, 2012

Estimating Thoughts of Suicide in Youth with ASD

J Autism Dev Disord
DOI 10.1007/s10803-017-3180-7

S.I. : AUTISM INPATIENT COLLECTION - STUDYING THE SEVERELY AFFECTED

Talking About Death or Suicide: Prevalence and Clinical Correlates in Youth with Autism Spectrum Disorder in the Psychiatric Inpatient Setting

Lisa M. Horowitz[1] · Audrey Thurm[2] · Cristan Farmer[2] · Carla Mazefsky[3] · Elizabeth Lanzillo[1] · Jeffrey A. Bridge[4] · Rachel Greenbaum[5] · Maryland Pao[1] · Matthew Siegel[6,7] · for the Autism and Developmental Disorders Inpatient Research Collaborative (ADDIRC)

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Abstract Little is known about suicidal ideation in youth with autism spectrum disorder (ASD), making it difficult to identify those at heightened risk. This study describes the prevalence of thoughts about death and suicide in 107 verbal youth with ASD with non-verbal IQ >55, assessed during inpatient psychiatric admission. Per parent report, 22% of youth with ASD had several day periods when they talked about death or suicide "often," or "very often." Clinical correlates included the presence of a comorbid mood (OR 2.71, 95% CI 1.12–6.55) or anxiety disorder (OR 2.32, 95% CI 1.10–4.93). The results suggest a need for developmentally appropriate suicide risk screening measures in ASD. Reliable detection of suicidal thoughts in this high-risk population will inform suicide prevention strategies.

Keywords Autism spectrum disorder · Suicide · Inpatient · Suicidal ideation · Psychiatric patients · Screening · Autism Inpatient Collection (AIC)

Introduction

Suicide is an international public health crisis and the second leading cause of death for youth aged 10–24 years (Centers for Disease Control and Prevention 2015; World Health Organization 2014). While individuals with a variety of psychiatric diagnoses are at heightened risk for suicide, recent studies suggest that youth with autism spectrum disorder (ASD) are at elevated risk (Bennett 2016;

Summary of Findings

- Frequency with which their child has had periods lasting several days where he or she "talks about death or suicide" (Child & Adolescent Symptom Inventory, item #86)
- N=107, 10 yrs +, mean of 13, NVIQ ≥55, ADOS-2 + ASD
- Per parent report, 23% of youth talked about death or suicide "often" or "very often"
- Comorbid diagnoses:
  - **Mood disorder** – nearly 3 times more likely (Odds ratio: 2.71, CI: 1.12-6.55)
  - **Anxiety disorder** – over 2 times more likely (Odds ratio: 2.30, CI: 1.08-4.91)
  - **ADHD** – less likely (Odds ratio: 0.45, CCI: 0.21-0.96)

Answering a Need

- **Previously validated scales may not be applicable**
- **We do not know how the ASQ functions in people with ASD**
- **We need to validate the instrument in the ASD population**

ASQ-ASD Multisite Instrument Development Study

NIH National Institute of Mental Health

Aim

- To test and adapt the ASQ for youth and adults with ASD

Instrument Development Study

- Collaboration with the Autism Developmental Disorders Inpatient Research Collaborative (ADDIRC)

- Sample: clients enrolled in the ADDIRC
  - Ages 12+
  - Diagnosed with ASD
  - Inpatient psychiatric treatment

Pilot Data

- Surrey Place Centre (Toronto, Ontario)

Summary

- Universal suicide risk screening for all youth in medical settings
- Clinicians require population-specific and site-specific validated screening instruments
- Youth with ASD at risk for suicide may go undetected, as there are no tools specifically created for ASD population
- We are currently testing the ASQ for implementation in the ASD population
- Screening studies can lead to evidence-based guidelines for screening and managing youth with ASD at risk for suicide

Thank you

- **Surrey Place Center**
  - Rachel Greenbaum, PhD and Laura Weinheimer
- **NIMH team**
  - Maryland Pao, MD
  - Audrey Thurm, PhD
  - Elizabeth Ballard, PhD
  - Erica Ludi, MD
  - Dan Powell, BA
  - Cristan Farmer, PhD
  - Eliza Lanzillo, BA
- **Autism Developmental Disorders Inpatient Research Collaborative**
  - Matthew Siegel, MD
  - Carla Mazefsky, PhD
- **Humbolt University**
  - William Reynolds, PhD
- **Nationwide Children's Hospital**
  - Jeffrey Bridge, PhD

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NIH National Institute of Mental Health

Aligning National Efforts to Prevent Suicide

Colleen Carr, Deputy Director, National Action Alliance for Suicide Prevention

24 October 2017

Support for the Secretariat of the National Action Alliance for Suicide Prevention is provided by The Suicide Prevention Resource Center at EDC through a grant from the U.S. Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Mental Health Services (CMHS), under Grant No. 5U79SM062297.

The views, opinions, and content expressed in this product do not necessarily reflect the views, opinions, or policies of CMHS, SAMHSA, or HHS.

Overview:

- The nation’s public-private partnership for suicide prevention
- National suicide prevention resources

The National Action Alliance for Suicide Prevention

The Nation's Public-Private Partnership for Suicide Prevention

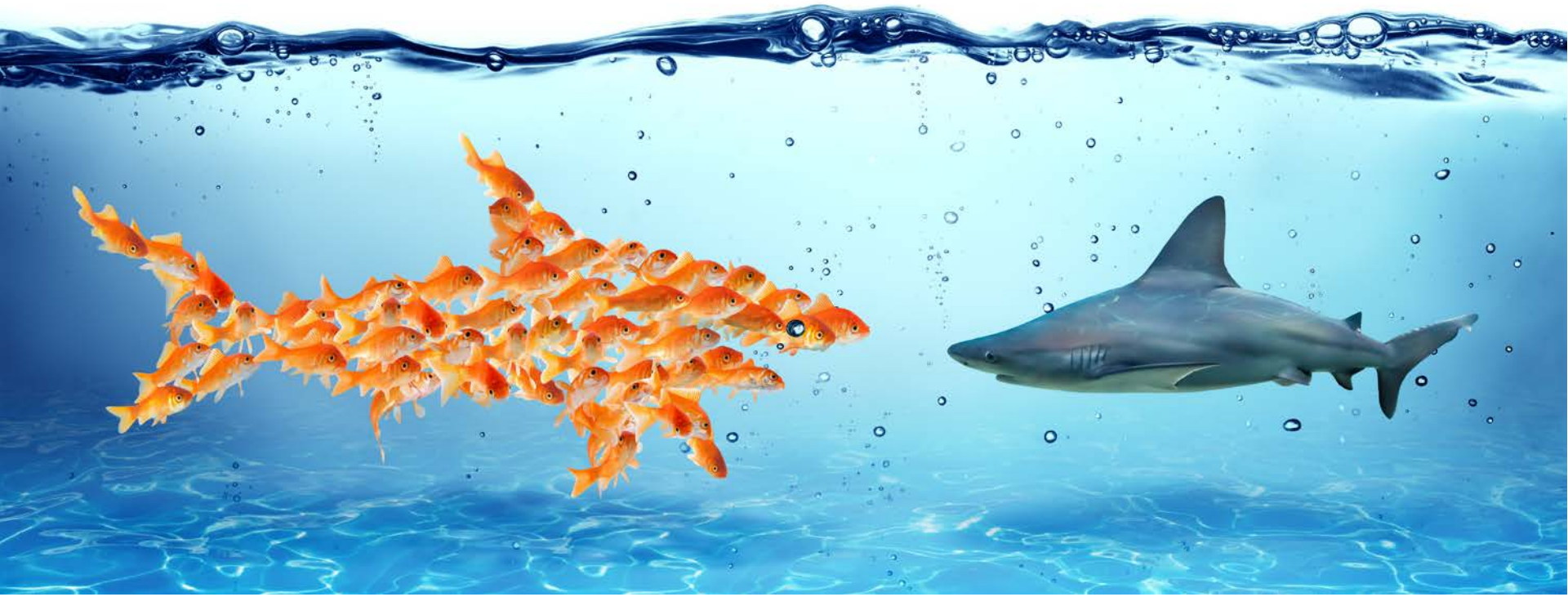
Action Alliance Overview

We are…

the nation's public-private partnership for suicide prevention.

We engage more than 250 public and private organizations to advance implementation of the National Strategy for Suicide Prevention

TOGETHER we can do so much.



Action Alliance Overview

Mission:

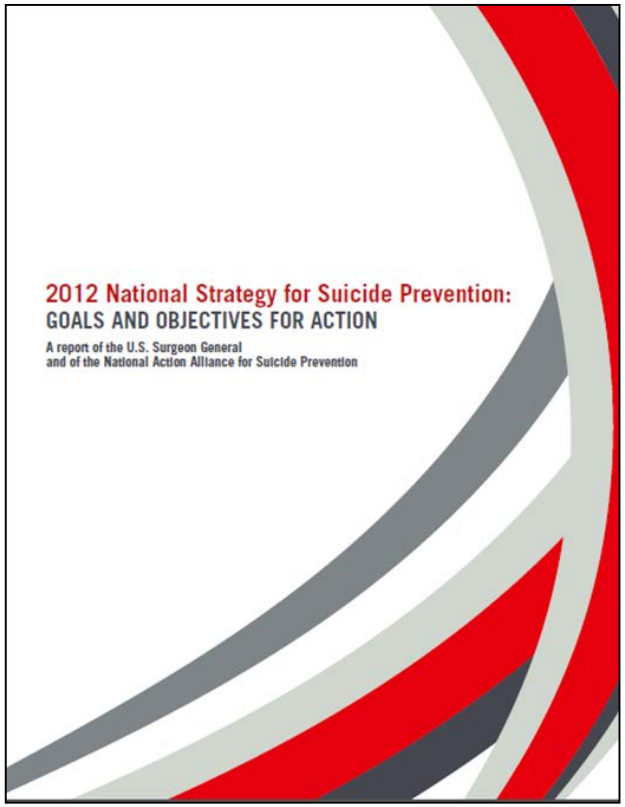
- **Champion** suicide prevention as a national priority.
- **Catalyze** efforts to implement high-priority objectives from the *National Strategy for Suicide Prevention.*
- **Cultivate** the resources needed to sustain progress.

Goal:

- To reduce annual suicide rate **20 percent by 2025.**

Action Alliance Overview

We are committed to advancing the *National Strategy for Suicide Prevention*



Action Alliance Overview

Executive Committee Co-chairs:

- **Public Sector**:
  Dr. Carolyn M. Clancy
  Executive in Charge, Veterans Health Administration
  U.S. Department of Veteran Affairs

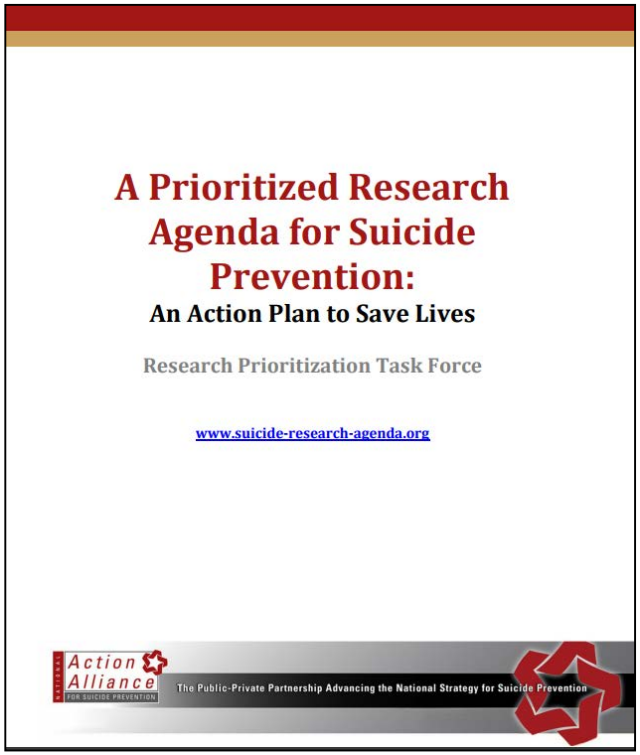
- **Private Sector**:
  Mr. Robert W. Turner
  Senior Vice President – Retired
  Union Pacific Corporation


EDC Learning transforms lives.
UHS
Johnson & Johnson
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
eic
Entertainment Industries Council, Inc.
INTERNATIONAL ASSOCIATION OF CHIEFS OF POLICE
POLICE
SINCE 1893
Substance Abuse and Mental Health Services Administration
SAMHSA
DEPARTMENT OF DEFENSE
UNITED STATES OF AMERICA
The National Public-Private Partnership for Suicide Prevention
facebook
AMERICAN FOUNDATION FOR Suicide Prevention
NFL
CADCA
MENTAL HEALTH FIRST AID
NATIONAL COUNCIL FOR BEHAVIORAL HEALTH
Healthy Minds. Strong Communities.
U.S. Department of Veterans Affairs
THE KENNEDY FORUM
UNION PACIFIC
KAISER PERMANENTE

Action Alliance Overview

Prioritized Research Agenda:

NSSP Objective 12.1: Develop a national suicide prevention research agenda.

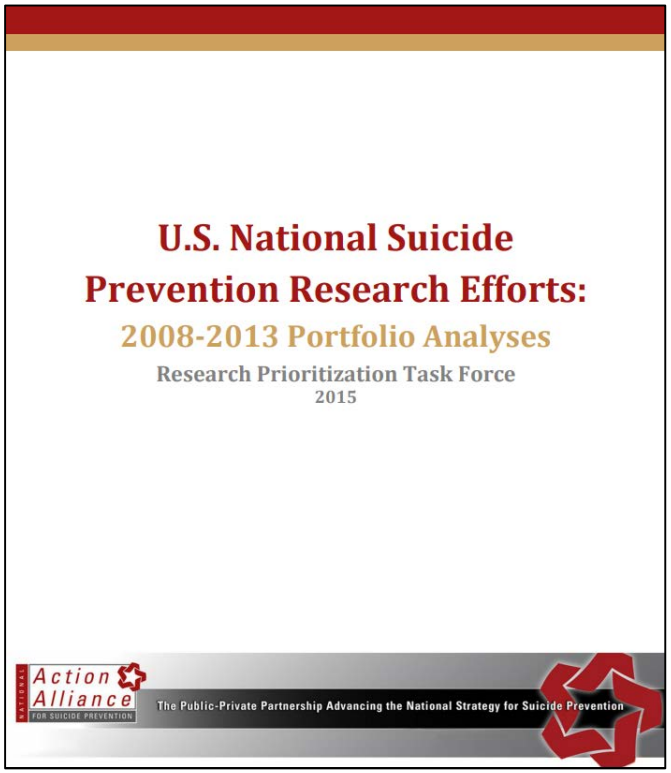


Key Question 1: Why do people become suicidal?
Key Question 2: How can we better or more optimally detect/predict risk?
Key Question 3: What interventions prevent individuals from engaging in suicidal behavior?
Key Question 4: What services are most effective for treating the suicidal person and prevention suicidal behavior?
Key Question 5: What other types of interventions (outside health care settings) reduce suicide risk?
Key Question 6: What new and existing research infrastructure is needed to reduce suicidal behavior?

Action Alliance Overview

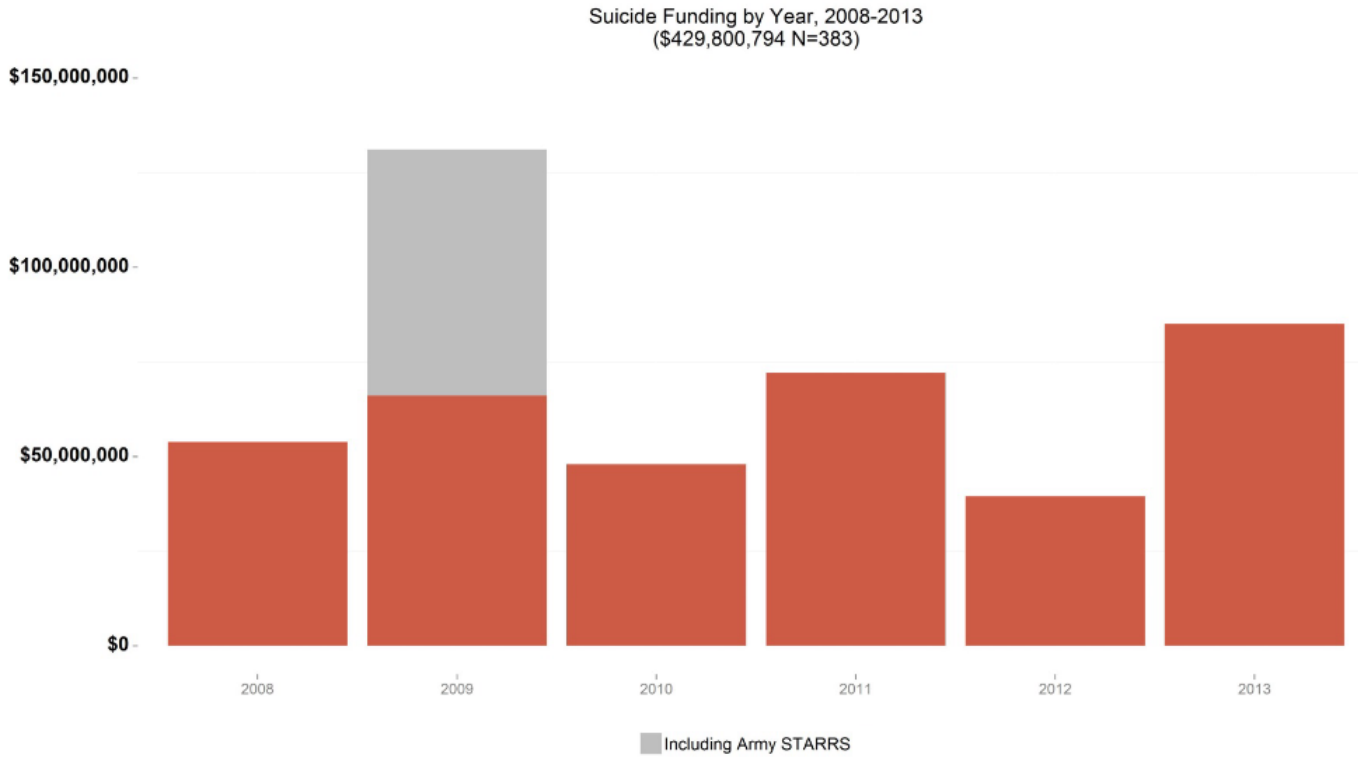
Suicide Prevention Research Portfolio Analyses

NSSP Objective 12.2: Disseminate the national suicide prevention research agenda, inventory funded suicide research.



Action Alliance Overview

Figure 7: U.S. Suicide Research Funding by Fiscal Year, 2008–2013



- The average annual combined investment in suicide research is $71.6 million per year (between 2008-2013), inclusive of Army STARRS ($60.8 million excluding Army STARRS)

Source: U.S. National Suicide Prevention Research Efforts: 2008-2013, Portfolio Analyses, Action Alliance.

Action Alliance Overview

- The Action Alliance is committed to:
  - Reaching at-risk populations (e.g., American Indian/Alaska Native, veterans and military servicemembers, suicide attempt survivors, and survivors of suicide loss)
  - Engaging individuals with lived experience to inform and enhance future prevention strategies

"For too long the voice of millions of suicide attempt survivors, like myself, and the value of our experience has been discounted. Now we have come together to provide what could be the most meaningful and impactful contributors to reducing suicide- lived experience"

- **- Eduardo Vega (Co-Lead, Action Alliance Suicide Attempt Survivor Task Force)**

Action Alliance Overview

Transforming Health Systems

NSSP GOAL 8. Promote suicide prevention as a core component of health care.

We bring together national leaders and implement strategies to improve:

- Acute care transitions
- Standards of care
- Clinical workforce preparedness
- Crisis services
- Financing
- Zero Suicide

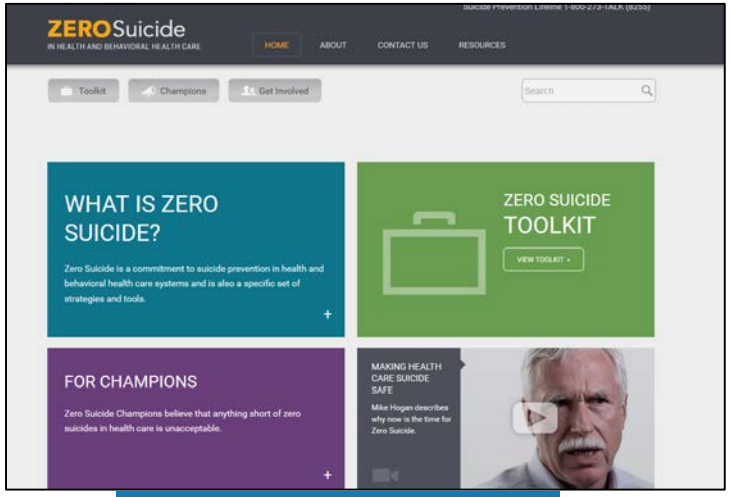
"Over the decades, individual (mental health) clinicians have made heroic efforts to save lives…but system of care have done very little"
Dr. Richard McKeon

Action Alliance Overview

Zero Suicide Initiative

NSSP Objective 8.1: Promote the adoption of "zero suicides" as an aspirational goal by health care and community support systems that provide services and support to defined patient populations.

The Action Alliance launched, and is now scaling up implementation of, the **Zero Suicide initiative** an evidence-informed quality improvement approach to improving suicide care in health and behavioral health care systems



zerosuicide.sprc.org

"Suicide represents a worst case failure in mental health care. We must work to make it a 'never event in our programs and systems of care"
- Dr. Mike Hogan

Action Alliance Overview

Changing the Conversation

NSSP GOAL 4. Promote responsible media reporting of suicide, accurate portrayals of suicide and mental illnesses in the entertainment industry, and the safety of online content related to suicide.

We leverage news reporters, entertainment industry representatives, and suicide prevention messengers to change the national narratives around suicide and suicide prevention to ones that promote:

- Hope
- Connectedness
- Social support
- Resilience
- Treatment
- Recovery

Action Alliance Overview

Transforming Communities

NSSP Goal 1. Integrate and coordinate suicide prevention activities across multiple sectors and settings.

We support suicide prevention efforts to reach individuals at risk who are not engaged with the health system. We engage faith community leaders, workplaces, and other community settings to be part of the community suicide prevention response.

Faith. Hope. Life. Celebrating Reasons to Live

Suicide Prevention Resources

Suicide Prevention Resources

SPRC • Suicide Prevention Resource Center

Promoting a public health approach to suicide prevention

Assessing and Managing Suicide Risk (AMSR)

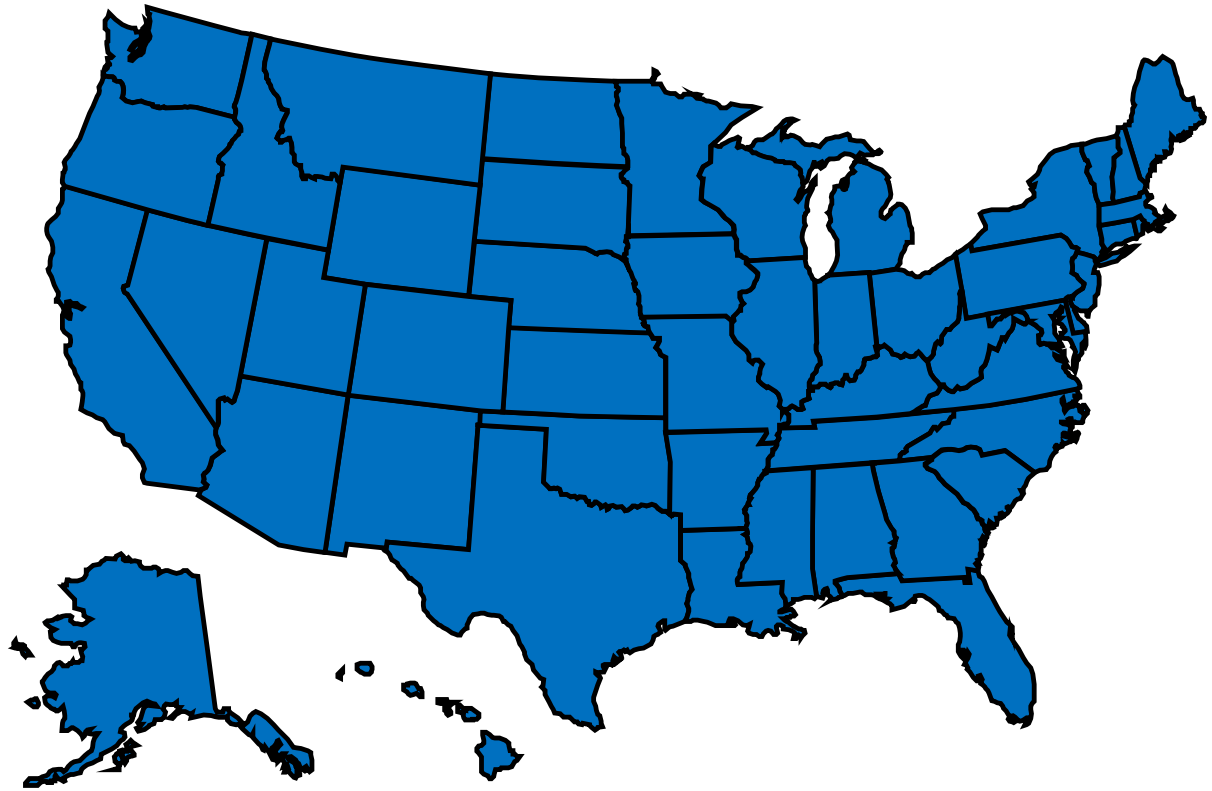
Core Competencies for Behavioral Health Professionals

Suicide Prevention Resources

- 24/7, free and confidential support for people in distress.
- Prevention and crisis resources.
- Best practices for professionals.

Suicide Prevention Resources

Local/State Suicide Prevention Coordinators



Suicide Prevention Resources

The Suicide Prevention Resource Center (SPRC) is the nation's only federally supported resource center devoted to advancing the National Strategy for Suicide Prevention. SPRC is funded by the Substance Abuse and Mental Health Services Administration (SAMHSA)

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www.actionallianceforsuicideprevention.org

Meeting of the IACC

Afternoon Agenda

3:30	**Committee Discussion**
4:00	**Afternoon Break**
4:15	**Summary of Advances Discussion**

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

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Meeting of the IACC

Committee Discussion

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IACC
INTERAGENCY AUTISM
COORDINATING COMMITTEE

Break

Meeting of the IACC

Afternoon Agenda

4:15 **Summary of Advances Discussion**

Susan Daniels, Ph.D.
Director, OARC, NIMH and Executive Secretary, IACC

Joshua Gordon, M.D., Ph.D.
Director, NIMH and Chair, IACC

4:45 **Round Robin**

5:00 **Closing Remarks and Adjournment**

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2017 Summary of Advances Nominations
April – October 2017

Joshua A. Gordon, M.D., Ph.D.
Director, National Institute of Mental Health
Chair, IACC

Question 1: Screening and Diagnosis

Science Translational Medicine

Jun 2017

Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age.

Emerson RW, Adams C, Nishino T, Hazlett HC, Wolff JJ, Zwaigenbaum L, Constantino JN, Shen MD, Swanson MR, Elison JT, Kandala S, Estes AM, Botteron KN, Collins L, Dager SR, Evans AC, Gerig G, Gu H, McKinstry RC, Paterson S, Schultz RT, Styner M; IBIS Network, Schlaggar BL, Pruett JR Jr, Piven J

The International Journal of Research and Practice Volume 21 Number 5 July 2017

autism

Aug 2017

Behavioural and cognitive sex/gender differences in autism spectrum condition and typically developing males and females.

Hull L, Mandy W, Petrides KV

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Question 1: Screening and Diagnosis

Official Journal of the Society of Biological Psychiatry
Biological Psychiatry

Aug 2017

The emergence of network inefficiencies in infants with autism spectrum disorder.
Kostopoulos P, Gerig G, Dager SR, Paterson S, Schultz RT, Styner MA, Hazlett HC, Piven J; Infant Brain Imaging Study Network

The Journal of Child Psychology and Psychiatry

Oct 2017

Evaluating social (pragmatic) communication disorder.
Mandy W, Wang A, Lee I, Skuse D

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Question 2: Biology

nature

Jul 2017

Infant viewing of social scenes is under genetic control and is atypical in autism.
Constantino JN, Kennon-McGill S, Weichselbaum C, Marrus N, Haider A, Glowinski AL, Gillespie S, Klaiman C, Klin A, Jones W

Molecular Autism

Apr 2017

Neurogenetic analysis of childhood disintegrative disorder.
Gupta AR, Westphal A, Yang DYJ, Sullivan CAW, Eilbott J, Zaidi S, Voos A, Vander Wyk BC, Ventola P, Waqar Z, Fernandez TV, Ercan-Sencicek AG, Walker MF, Choi M, Schneider A, Hedderly T, Baird G, Friedman H, Cordeaux C, Ristow A, Shic F, Volkmar FR, Pelphrey KA

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Question 2: Biology

Cerebral CORTEX

Mar 2017

Cortical thickness abnormalities in autism spectrum disorders through late childhood, adolescence, and adulthood: a large-scale MRI study.
Khundrakpam BS, Lewis JD, Kostopoulos P, Carbonell F, Evans AC

JAMA Pediatrics

Sep 2017

Association of sex with recurrence of autism spectrum disorder among siblings.
Palmer N, Beam A, Agniel D, Eran A, Manrai A, Spettell C, Steinberg G, Mandl K, Fox K, Nelson SF, Kohane I

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Question 3: Risk Factors

Jun 2017

Fetal and postnatal metal dysregulation in autism.
Arora M, Reichenberg A, Willfors C, Austin C, Gennings C, Berggren S, Lichtenstein P, Anckarsäter H, Tammimies K, Bölte S

Aug 2017

Hotspots of missense mutation identify neurodevelopmental disorder genes and functional domains.
Geisheker MR, Heymann G, Wang T, Coe BP, Turner TN, Stessman HAF, Hoekzema K, Kvarnung M, Shaw M, Friend K, Liebelt J, Barnett C, Thompson EM, Haan E, Guo H, Anderlid BM, Nordgren A, Lindstrand A, Vandeweyer G, Alberti A, Avola E, Vinci M, Giusto S, Pramparo T, Pierce K, Nalabolu S, Michaelson JJ, Sedlacek Z, Santen GWE, Peeters H, Hakonarson H, Courchesne E, Romano C, Kooy RF, Bernier RA, Nordenskjöld M, Gecz J, Xia K, Zweifel LS, Eichler EE

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Question 3: Risk Factors

Apr 2017

Grand-maternal smoking in pregnancy and grandchild's autistic traits and diagnosed autism.
Golding J, Ellis G, Gregory S, Birmingham K, Iles-Caven Y, Rai D, Pembrey M

Sep 2017

Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring.
Kim S, Kim H, Yim YS, Ha S, Atarashi K, Tan TG, Longman RS, Honda K, Littman DR, Choi GB, Huh JR

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Question 3: Risk Factors

AUTISM RESEARCH

Apr 2017 [Epub ahead of print]

The joint effect of air pollution exposure and copy number variation on risk for autism.

Kim D, Volk H, Girirajan S, Pendergrass S, Hall MA, Verma SS, Schmidt RJ, Hansen RL, Ghosh D, Ludena-Rodriguez Y, Kim K, Ritchie MD, Hertz-Picciotto I, Selleck SB

nature neuroscience

Jul 2017

Rates, distribution and implications of postzygotic mosaic mutations in autism spectrum disorder.

Lim ET, Uddin M, De Rubeis S, Chan Y, Kamumbu AS, Zhang X, D'Gama AM, Kim SN, Hill RS, Goldberg AP, Poultney C, Minshew NJ, Kushima I, Aleksic B, Ozaki N, Parellada M, Arango C, Penzol MJ, Carracedo A, Kolevzon A, Hultman CM, Weiss LA, Fromer M, Chiocchetti AG, Freitag CM; Autism Sequencing Consortium, Church GM, Scherer SW, Buxbaum JD, Walsh CA

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Question 3: Risk Factors

Molecular Autism

Jan 2017

Serum and cerebrospinal fluid immune mediators in children with autistic disorder: a longitudinal study.
Pardo CA, Farmer CA, Thurm A, Shebl FM, Ilieva J, Kalra S, Swedo S

Cell

Sep 2017

Genomic patterns of de novo mutation in simplex autism.
Turner TN, Coe BP, Dickel DE, Hoekzema K, Nelson BJ, Zody MC, Kronenberg ZN, Hormozdiari F, Raja A, Pennacchio LA, Darnell RB, Eichler EE

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Question 3: Risk Factors

PSYCHOLOGICAL MEDICINE

May 2017 [Epub ahead of print]

Autism risk following antidepressant medication during pregnancy.
Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S

nature genetics

May 2017 [Epub ahead of print]

Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders.
Weiner DJ, Wigdor EM, Ripke S, Walters RK, Kosmicki JA, Grove J, Samocha KE, Goldstein JI, Okbay A, Bybjerg-Grauholm J, Werge T, Hougaard DM, Taylor J; iPSYCH-Broad Autism Group; Psychiatric Genomics Consortium Autism Group, Skuse D, Devlin B, Anney R, Sanders SJ, Bishop S, Mortensen PB, Børglum AD, Smith GD, Daly MJ, Robinson EB

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Question 4: Treatments and Inteventions

AUTISM RESEARCH

Jun 2017

Cross-site randomized control trial of the Social ABCs caregiver-mediated intervention for toddlers with autism spectrum disorder.
Brian JA, Smith IM, Zwaigenbaum L, Bryson SE

BEHAVIORAL DEVELOPMENT BULLETIN

Apr 2017

Measuring developmental outcomes in autism spectrum disorder (ASD).
Commons ML, Adhikari D, Giri S, Weinberg M, Baran JJ, Malik E

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Question 4: Treatments and Interventions

The International Journal of Research and Practice
Volume 21 Number 5 July 2017
autism

Apr 2017

Changes in anxiety following a randomized control trial of a theatre-based intervention for youth with autism spectrum disorder.
Corbett BA, Blain SD, Ioannou S, Balser M

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

May 2017

Nutritional and dietary interventions for autism spectrum disorder: a systematic review.
Sathe N, Andrews JC, McPheeters ML, Warren ZE

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Question 4: Treatments and Interventions

The Journal of Child Psychology and Psychiatry

May 2017

Hybrid implementation model of community-partnered early intervention for toddlers with autism: a randomized trial.
Shire SY, Chang YC, Shih W, Bracaglia S, Kodjoe M, Kasari C

Jun 2017

Four-year follow-up of children in the LEAP Randomized Trial: some planned and accidental findings.
Strain PS

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Question 4: Treatments and Interventions

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

May 2017 [Epub ahead of print]

Interventions targeting sensory challenges in autism spectrum disorder: a systematic review.
Weitlauf AS, Sathe N, McPheeters ML, Warren ZE

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Question 5: Services

Health Affairs

Oct 2017

Effects of state insurance mandates on health care use and spending for autism spectrum disorder.
Barry CL, Epstein AJ, Marcus SC, Kennedy-Hendricks A, Candon MK, Xie M, Mandell DS

EVALUATION and PROGRAM PLANNING

Jun 2017

Implementation evaluation of early intensive behavioral intervention programs for children with autism spectrum disorders: A systematic review of studies in the last decade.
Caron V, Bérubé A, Paquet A

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Question 5: Services

Jun 2017

Comparisons of self-determination among students with autism, intellectual disability, and learning disabilities: a multivariate analysis.
Chou Y, Wehmeyer ML, Palmer SB, Lee J

Sep 2017

Cost offset associated with Early Start Denver Model for children with autism.
Cidav Z, Munson J, Estes A, Dawson G, Rogers S, Mandell D

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Question 5: Services

Journal of Autism and Developmental Disorders

May 2017

Examining the efficacy of a family peer advocate model for black and hispanic caregivers of children with autism spectrum disorder.
Jamison JM, Fourie E, Siper PM, Trelles MP, George-Jones J, Buxbaum Grice A, Krata J, Holl E, Shaoul J, Hernandez B, Mitchell L, McKay MM, Buxbaum JD, Kolevzon A

HealthAffairs

Feb 2017

Medicaid waivers targeting children with autism spectrum disorder reduce the need for parents to stop working.
Leslie DL, Iskandarani K, Velott DL, Stein BD, Mandell DS, Agbese E, Dick AW

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Question 5: Services

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

May 2017

Disparities in diagnosis and treatment of autism in Latino and non-Latino white families.
Zuckerman KE, Lindly OJ, Reyes NM, Chavez AE, Macias K, Smith KN, Reynolds A

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Question 6: Lifespan Issues

REHABILITATION COUNSELING BULLETIN

May 2017

Vocational rehabilitation service patterns: an application of social network analysis to examine employment outcomes of transition-age individuals with autism.
Ditchman NM, Miller JL, Easton AB

Journal of Autism and Developmental Disorders

Sep 2017

Brief report: postsecondary work and educational disruptions for youth on the autism spectrum.
Taylor JL, DaWalt LS

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Question 6: Lifespan Issues

Journal of Autism and Developmental Disorders

Jun 2017

Social media use, friendship quality, and the moderating role of anxiety in adolescents with autism spectrum disorder.

Van Schalkwyk GI, Marin CE, Ortiz M, Rolison M, Qayyum Z, McPartland JC, Lebowitz ER, Volkmar FR, Silverman WK

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Question 7: Infrastructure

AJPH

Nov 2017

Autism spectrum disorder among US children (2002-2010): socioeconomic, racial, and ethnic disparities.
Durkin MS, Maenner MJ, Baio J, Christensen D, Daniels J, Fitzgerald R, Imm P, Lee LC, Schieve LA, Van Naarden Braun K, Wingate MS, Yeargin-Allsopp M

American Journal of Epidemiology

May 2017

Geographic patterns of autism spectrum disorder among children of Nurses' Health Study II women.
Hoffman K, Weisskopf MG, Roberts AL, Raz R, Hart JE, Lyall K, Hoffman EM, Laden F, Vieira VM

These slides do not reflect decisions of the IACC and are for discussion purposes only.

Question 7: Infrastructure

Journal of the American Academy of Child & Adolescent Psychiatry

Jun 2017

What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis.
Loomes R, Hull L, Mandy WPL

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Meeting of the IACC

Round Robin

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Autism Centers of Excellence (ACE): Program Update

Alice Kau, PhD
Program Director, NICHD

October 24, 2017

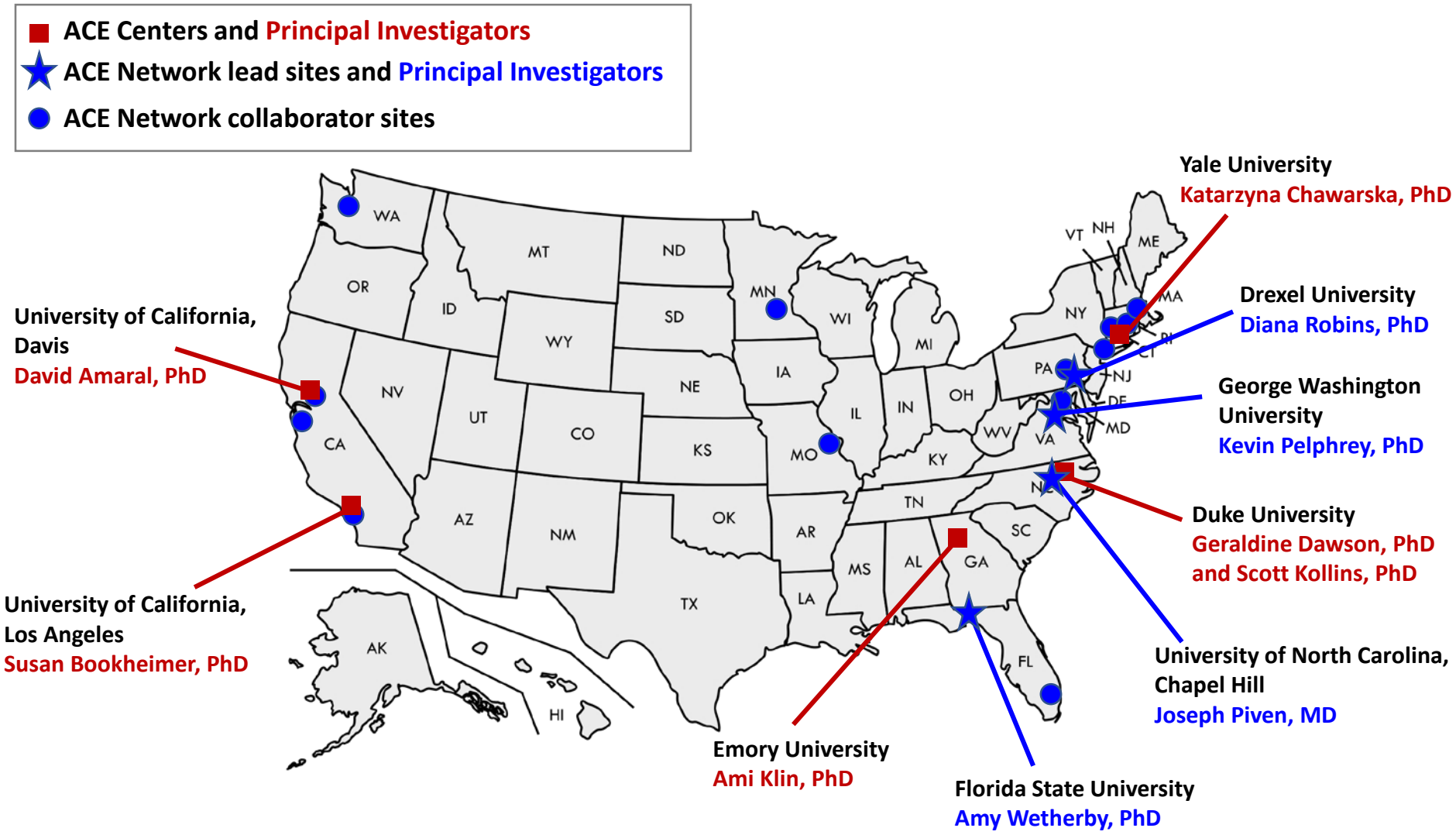
Autism Centers of Excellence Program

- Supports large research projects aimed at understanding ASD and developing interventions
- Encourages innovative, multi-disciplinary research
- Awardees required to collect data using common methods and to submit all data to the NIH's centralized National Database for Autism Research (NDAR)
- ACE Centers (research at individual institutions) and ACE Networks (research at multiple institutions)

New ACE Awards

- 9 new awards (5 Centers and 4 Networks) for 3rd award cycle of program
- Total nearly $100M over the next 5 years
- Jointly funded by:
  - **NICHD** – *Eunice Kennedy Shriver* National Institute for Child Health and Human Development
  - **NIDCD** – National Institute of Deafness and Other Communication Disorders
  - **NIEHS** – National Institute on Environmental Health Sciences
  - **NIMH** – National Institute for Mental Health
  - **NINDS** – National Institute for Neurological Disorders and Stroke

New ACE Awards



Not shown: University of Alberta and McGill University-Montreal Neurological Institute

New ACE Awards - Centers

Improving ASD treatments based on symptoms, features
PI: David G. Amaral, Ph.D.
University of California, Davis

Tracing ASD symptoms to their origins
PI: Susan Bookheimer, Ph.D.
University of California, Los Angeles

Examining development of functional brain connections
PI: Katarzyna Chawarska, Ph.D.
Yale University

Understanding and potentially treating ASD-ADHD combination
Co-PIs: Geraldine Dawson, Ph.D. and Scott Kollins, Ph.D.
Duke University

Studying social interaction to identify the early signs of ASD
PI: Ami Klin, Ph.D.
Emory University

New ACE Awards - Networks

Investigating how ASD differs between boys and girls
PI: Kevin Pelphrey, Ph.D.
George Washington University

Tracking brain development, behavior as ASD progresses
PI: Joseph Piven, M.D.
University of North Carolina, Chapel Hill

Evaluating autism screening for all toddlers
PI: Diana L. Robins, Ph.D.
Drexel University

Testing parent coaching, home intervention for toddlers
PI: Amy Wetherby, Ph.D.
Florida State University

Meeting of the IACC

Closing Remarks

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Meeting of the IACC

Adjournment

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