Meeting of the Interagency Autism Coordinating Committee

January 12, 2016

National Institutes of Health
31 Center Drive
Building 31, C Wing, 6th Floor, Conference Room 6
Bethesda, MD 20892

Conference Call Access:
Phone: (800) 988-9744
Access Code: 3700810

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**

Bruce Cuthbert, Ph.D.
Acting Director, NIMH and Chair, IACC

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

Meeting of the IACC

Morning Agenda

9:15 AM **Research Domain Criteria (RDoC): An Overview**

Bruce Cuthbert, Ph.D.
Acting Director, NIMH and Chair, IACC

9:30 **The Autism Biomarkers Consortium for Clinical Trials**

James C. McPartland, Ph.D.
Associate Professor of Child Psychiatry and Psychology, Yale Child Study Center

Research Domain Criteria (RDoC): An Overview

IACC

Bruce N. Cuthbert, Ph. D.

Acting Director

National Institute of Mental Health

12 January 2016

National Institute of Mental Health

NIMH RDoC Workgroup Members

- Bruce Cuthbert (head)
- Sarah Morris (acting head)
- Rebecca Garcia, DEA
- Marjorie Garvey, DDTR
- Marlene Guzman, OD
- Robert Heinssen, DSIR
- Arina Kadam, RDoC
- Michael Kozak, DTR
- Kristina McLinden, DTR
- Kristina McLinden, DTR
- Jenni Pacheco, RDoC
- Daniel Pine, DIRP
- Kevin Quinn, OSPPC
- Matt Rudorfer, DSIR
- Charles Sanislow, Wesleyan University
- Janine Simmons, DNBBS
- Uma Vaidyanathan, RDoC

Why RDoC?

- Unremitting public health burden of mental disorders
- Current practices in clinical diagnosis (DSM, ICD) are no longer optimal for contemporary research.
- Diagnosis remains restricted to symptoms and signs, disorders are broad syndromes.
- Symptom-based approach hampers prevention.
- ***Problem: While sufficient for current clinical use, DSM/ICD categories also drive the entire research system (research grants, journals, trials, regulatory).***

The three traditional autism factors

- Alterations in social cognition, social behavior
- Communication impairment
- Repetitive interests, behaviors, and activities
- Factors correlate weakly (for a given symptom, only 20-40% have two symptoms; London, *Trends in Neurosciences*, 2014)

The experts weigh in

- Gillberg: "ESSENCE" (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations)
- London: need for alternative diagnoses in ASD, e.g., "developmental brain disorder" (London, *Trends in Neurosci*, 2014)
- Hyman: "makes sense to lump neurodevelopmental disorders for now, … to give researchers a chance to start over again, free of the bias created by current unwarranted splits." (spectrumnews.org)
- Lai, … Baron-Cohen, 2013: "autism is not homogeneous, and defining it using the umbrella term ASD risks whitewashing the evident heterogeneity, which has a substantial impact for research into this condition." (PLoS Biology, 2013)

Waterhouse & Gillberg: "Taking Autism Apart"

- (1) "Relinquish the belief that a single defining ASD brain dysfunction exists" (ignores individual variation)
- (2) Reduce the noise caused by thorny brain-symptom inference problems ("exploring very narrowly partitioned subgroups")
- "Conduct analyses of individual variation in brain measures" (e.g. Campbell et al 2013; three distinct genomic groups: disrupted neuron development, impaired nitric oxide signaling, impaired skeletal development pathways)

Toward the Future

- Scientific research: study appropriate groups, dimensions
- What if our groups are not correct; what do we do then?
- Shift from diagnostic approaches based purely on broad syndromes, to those based upon other classifiers: genetics, behavior, neural systems activity, specific symptoms
- Important: must examine the **relationships** among these different aspects
- What is the right way to do this?
- Einstein: “If we knew what we were doing, we wouldn’t call it research!”

Example: Grouping by genetics

A Genotype-First Approach to Defining the Subtypes of a Complex Disease

Holly A. Stessman,[1] Raphael Bernier,[2] and Evan E. Eichler[1,3,*]
[1]Department of Genome Sciences, University of Washington, Seattle, WA 98195, USA
[2]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195, USA
[3]Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195, USA
*Correspondence: eee@gs.washington.edu
http://dx.doi.org/10.1016/j.cell.2014.02.002

Medical genetics typically entails the detailed characterization of a patient's phenotypes followed by genotyping to discover the responsible gene or mutation. Here, we propose that the systematic discovery of genetic variants associated with complex diseases such as autism are progressing to a point where a reverse strategy may be fruitful in assigning the pathogenic effects of many different genes and in determining whether particular genotypes manifest as clinically recognizable phenotypes. This "genotype-first" approach for complex disease necessitates the development of large, highly integrated networks of researchers, clinicians, and patient families, with the promise of improved therapies for subsets of patients.

872 Cell *156*, February 27, 2014 ©2014 Elsevier Inc.

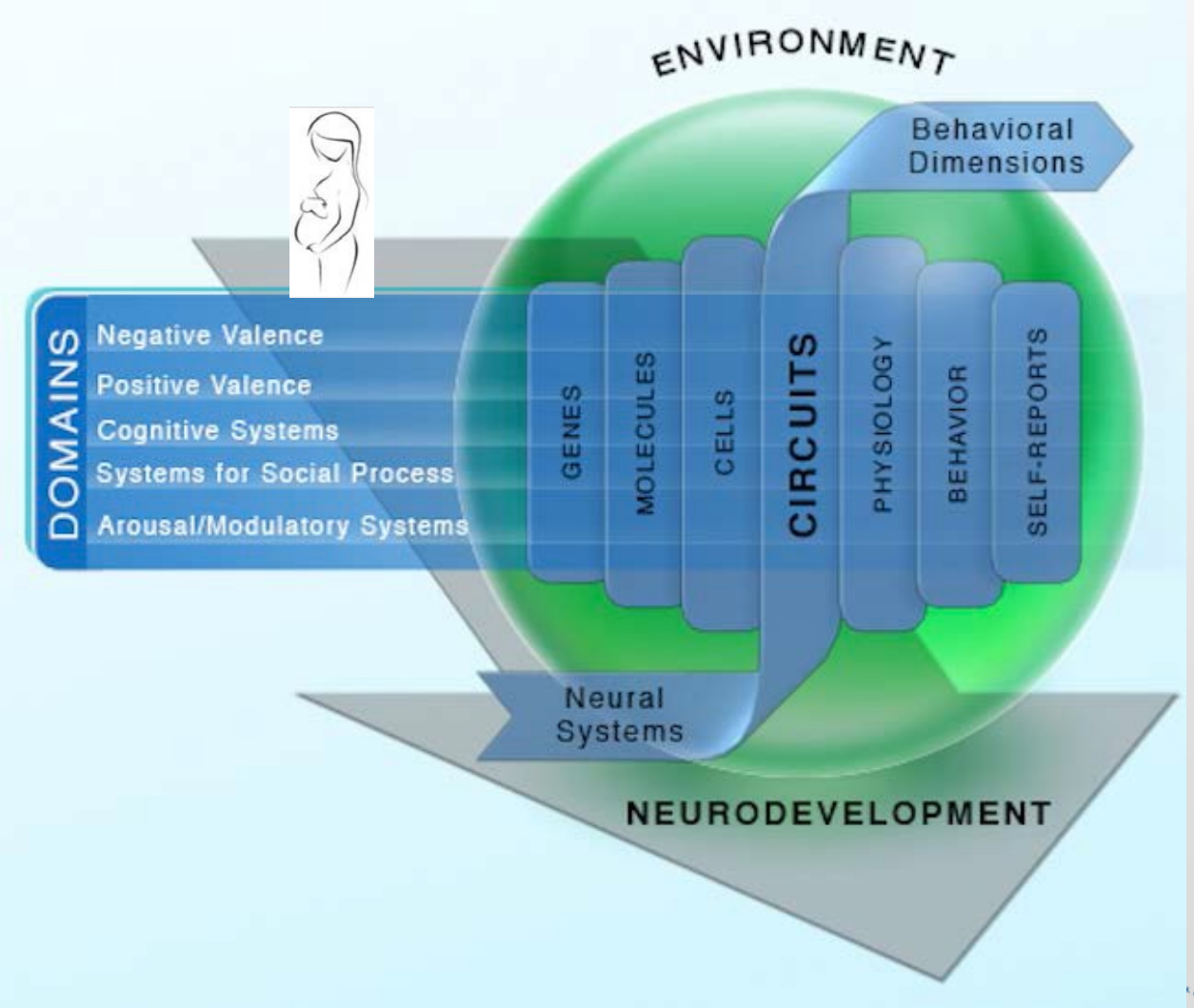
,

National Institute of Mental Health

How does RDoC fit in?

- Focused research initiative moving "toward a new classification system":
- Start with dimensional constructs related both to behavior and to brain systems (and that may cut across current diagnoses)
- Concept:
  1) Deeper understanding of psychological & biological systems related to mental illness →
  2) New biomarkers & biosignatures →
  3) More homogeneous groupings for psychopathology/pathophysiology →
  4) new intervention development

The RDoC Framework: Four dimensions



RDoC Matrix: Integrative Framework (Workshops July 2010 – June 2012)

v. 5.1, 07/15/2012	RESEARCH DOMAIN CRITERIA MATRIX							
	UNITS OF ANALYSIS							
DOMAINS/CONSTRUCTS	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social Communication								
Perception/Understanding of Self								
Perception/Understanding of Others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

[Symptoms]

- Altered Stress Reactivity
- Emotion regulation problems
- Lack of pleasure in usual activities
- Lack of energy for productive tasks
- Communication problems
- Executive function problems
- Social functioning impairments
- Poor relationships
- Problems with arousal-modulating systems
- Sleep problems

Dynamic: Always “Under Construction”

v. 5.1, 07/15/2012

RESEARCH DOMAIN CRITERIA MATRIX

UNITS OF ANALYSIS

DOMAINS/CONSTRUCTS	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Aro								
Arousal								
Biological rhythms								
Sleep-wake								

Psychological Medicine (2015), **45**, 2685–2689.
doi:10.1017/S0033291715000872

Updating the research domain criteria: the utility of a motor dimension

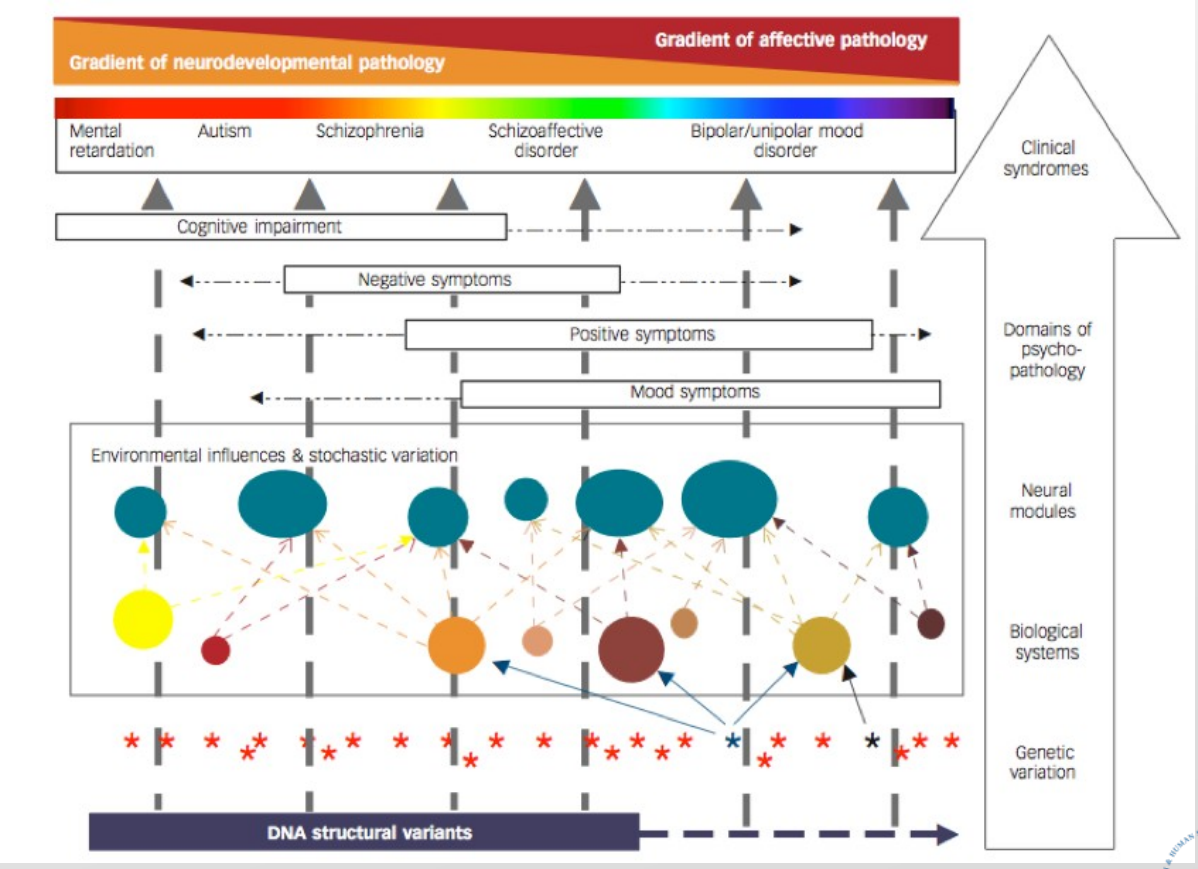
J. A. Bernard[1]* and V. A. Mittal[2]

[1] *Department of Psychology & Neuroscience, University of Colorado Boulder, Boulder, CO, USA*
[2] *Department of Psychology, Northwestern University, Evanston, IL, USA*

NIH National Institute of Mental Health

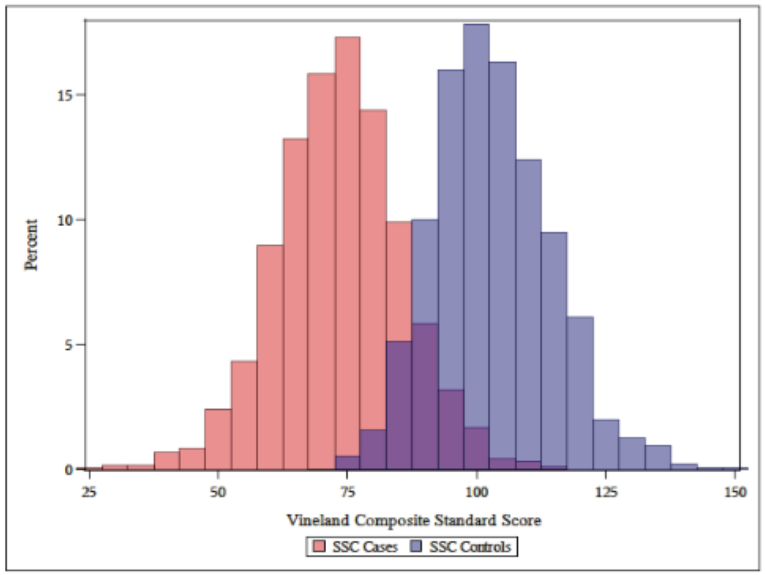
Contemporaneous Dimensional Approaches to Diagnosis

"Psychiatry will need to move from using traditional descriptive diagnoses to clinical entities (categories and/or dimensions) that relate more closely to the underlying workings of the brain." Craddock & Owen, *Br J Psych* (2010)



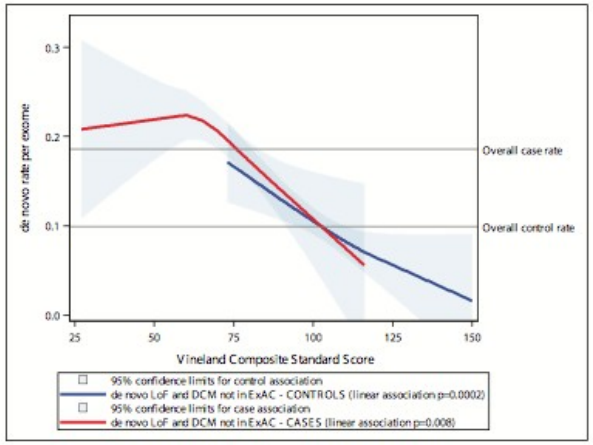
Continuity between neurotypical and ASD

Figure 2a. The distribution of Vineland scores overlaps between SSC cases and controls



Note: SSC= Simons Simplex Collection. The Vineland Composite Standard Score is normed, across ages, at mean 100, standard deviation 15 in the general population.

Figure 2b. *De novo* variation influences a continuum of functional outcomes in ASD cases and controls



Robinson et al., bioRxiv preprint, dx.doi.org/10.1101.027771

Ongoing RDoC Activities

- Develop tasks & instruments
- Common data elements
- NIMH data archives (NDAR)
- Data mining: seek more homogeneous dimensions, “microgroups” in large cohorts
- Regulatory agencies
- Goal: how do we best parse and understand the heterogeneity, to develop better treatment and preventive interventions?
- Precision medicine for ASD

ABC·CT

Autism Biomarkers Consortium for Clinical Trials

Project Overview

James McPartland, Ph.D.
Associate Professor, Yale Child Study Center Director,
Yale Developmental Disabilities Clinic

NATIONAL INSTITUTES OF HEALTH

SFARI
SIMONS FOUNDATION
AUTISM RESEARCH INITIATIVE

THE biomarkers CONSORTIUM

FNIH
Foundation for the
National Institutes of Health

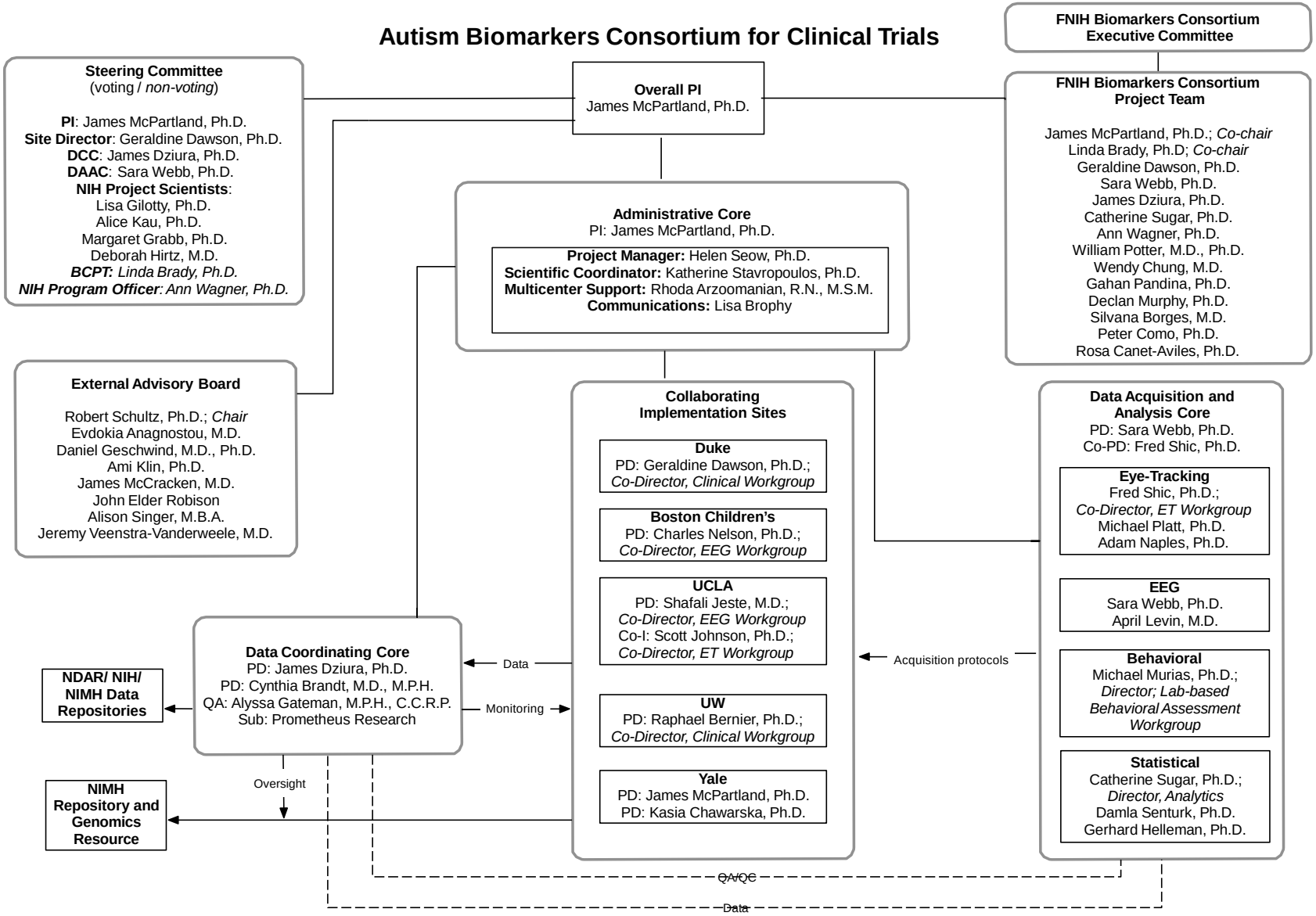
Scientific context for ABC-CT

- ASD is a complex neurodevelopmental disorder of unknown etiology, characterized by:
  - Difficulties with social-communication
  - Restricted, repetitive behaviors and interests and/or atypical sensory responsivity
- Heterogeneous clinical presentation
  - Symptom profile
  - Language
  - Cognitive ability
- Early stage evidence of social-communicative biomarkers
- The ABC-CT will provide methodologically rigorous multi-site evaluation of potential biomarkers in a large sample
  - Infrastructure designed to support future clinical trials

ABC-CT study design

- Multi-site, naturalistic study
  - *Administrative Core:* Yale
  - *Sites*: Duke, UCLA, UW, Boston Children's Hospital, Yale
  - *Data Coordinating Core*: YCCI, Prometheus
  - *Data Acquisition and Analysis Core*: SCRI, Duke, Yale, BCH, SiStat
- 4 to 11 year-old-children with ASD (N = 200) and typical development (TD; N = 75) with IQ 50-150
  - Feasibility study (25 ASD, 25 TD)
  - Three time points (Baseline, 6 weeks, 24 weeks)
- Potential biomarkers of social-communicative function
  - Eye tracking (~EU-AIMS)
  - EEG (~EU-AIMS)
  - Lab-based measures
- Commonly used clinician and caregiver assessments
- Blood draw for participant and parents

Autism Biomarkers Consortium for Clinical Trials



Sample characteristics: Inclusion/exclusion criteria

- ASD inclusion
  - ADOS, ADI, DSM-5
  - IQ 50-150
  - Medication stable 8 weeks
- ASD exclusion
  - Genetic/neurological
  - Epilepsy
  - Sensory/motor impairment
  - Metabolic/mitochondrial
  - Pre/perinatal
  - Environmental
  - Misc. invalidating factors
- TD inclusion
  - IQ 50-150
  - Medication stable 8 weeks
- TD exclusion
  - ASD/sibling with ASD
  - Genetic/neurological
  - Epilepsy
  - Sensory/motor impairment
  - Metabolic/mitochondrial
  - Misc. invalidating factors
  - Clinical score on CASI

ASD Biomarkers Project – Objectives

1. Compare sensitivity of objective indicators of social communicative function to conventional clinician and caregiver assessments with respect to clinical status
   - Correlations with clinical status at each time point and across time points
2. Evaluate potential utility of these measures, individually or in combination, as biomarkers for use in clinical trials
   - Feasibility of implementation; Construct validity; Test-retest reliability, consistency, and stability; Discriminant validity; Convergent validity; Sensitivity to change; Adequate variability within and between groups
3. Collect DNA samples for future genomic analyses and other potential analyses from all subjects, including parents of ASD subjects, to create a **community resource** of raw, processed, and analyzed data across modalities

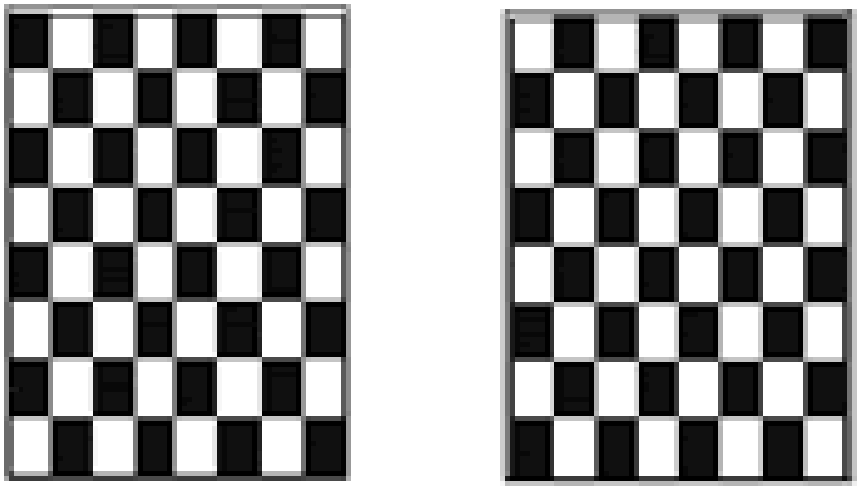
EEG Paradigms

EEG: Resting state

- Videos of non-social, abstract moving images
- Resting spectral power
  - Connectivity and coherence
  - Hemispheric asymmetry
  - Multiscale entropy
- Baseline for event-related EEG measures
- Discriminates ASD vs. TD in infants, children, adults
- Association with language ability

EEG: Visual evoked potentials

- Checkerboards reversing phase
- Low level visual processing
  - Functional integrity of visual pathway
  - Baseline for more complex (social) visual perceptual tasks

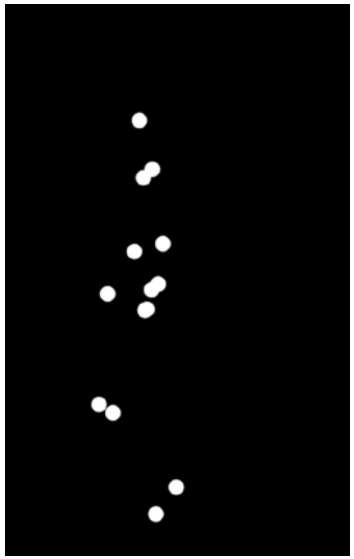


- Discriminates ASD vs. TD in infants

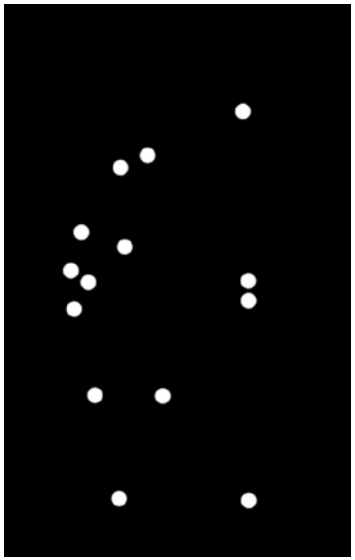
EEG: Biological motion

- Neural response to point light displays of human motion

Bio. motion



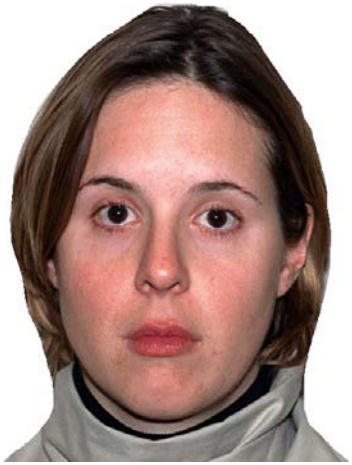
Scrambled



- Discriminates ASD vs. TD in school-aged children
  - Data collected across four study sites

EEG: Face processing

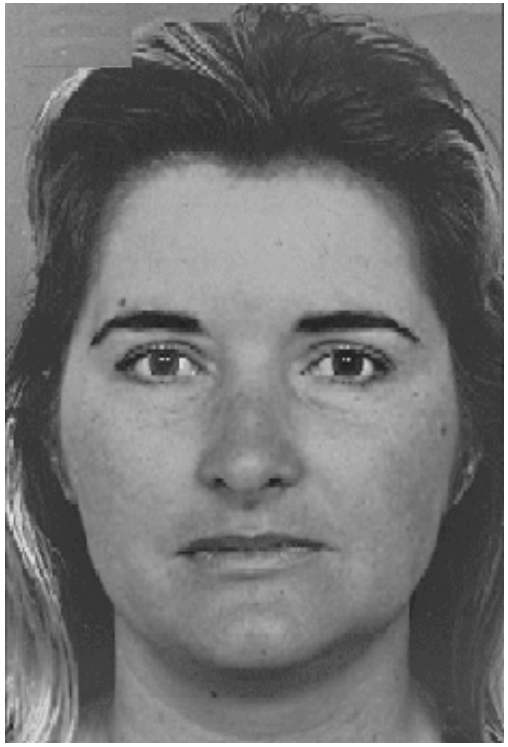
- EU-AIMS task
- Neural response to faces (vs. houses), inversion effect

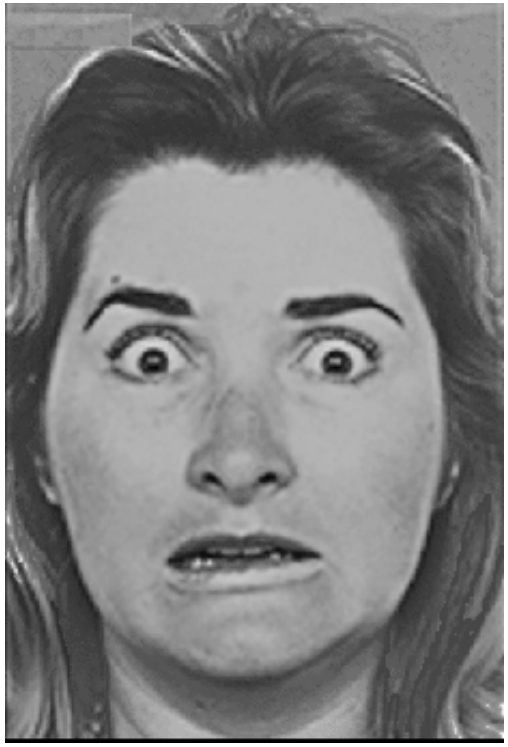


- Discriminates ASD vs. TD in HR infants, children, and adults
- Association with social and communicative function
- Sensitive to change in response to treatment

EEG: Emotional faces

- Neural response to neutral versus fearful expressions





- Discriminates ASD vs. TD in children and adults
- Association with social function

EEG: Social scenes

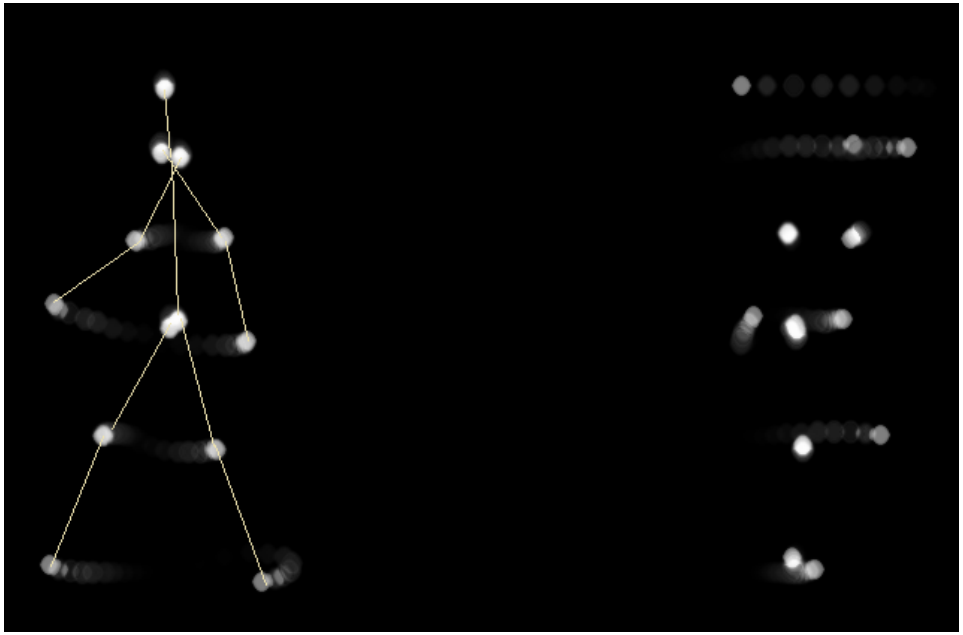
- EU-AIMS task
- Neural response to social and non-social dynamic scenes

- Discriminates ASD vs. TD in infants

Eye-tracking Paradigms

ET: Biological motion

- Overlap with EU-AIMS task
- Preferential attention to human motion



- Discriminates ASD vs. TD in toddlers through adults
- Collected across two study sites

ET: Spontaneous social orienting

- Response to bids for dyadic engagement, joint attention

- Discriminates ASD vs. TD in infants through preschool
- Stratification by developmental trajectory
- Associates with social function

ET: Activity monitoring

- Attention to shared social activity versus background distracters

- Discriminates ASD vs. TD in toddlers through adults
- Associates with social function
- Collected across two study sites

ET: Interactive social task

- Attention to naturalistic social activities between child partners

- Discriminates ASD vs. TD in school-aged children

ET: Dynamic naturalistic scenes

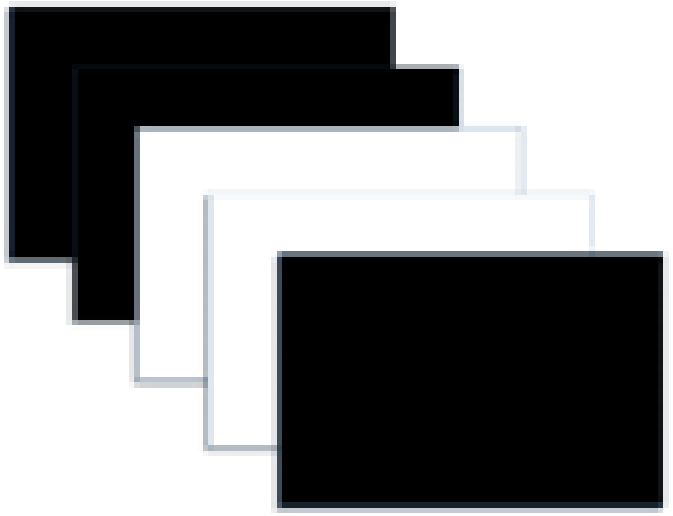
- Scanning patterns towards complex, dynamic social scenes

- Discriminates ASD vs. TD in school-aged children
- Scan patterns stratify children by social impairment
- Collected across two study sites

ET: Pupillary light reflex

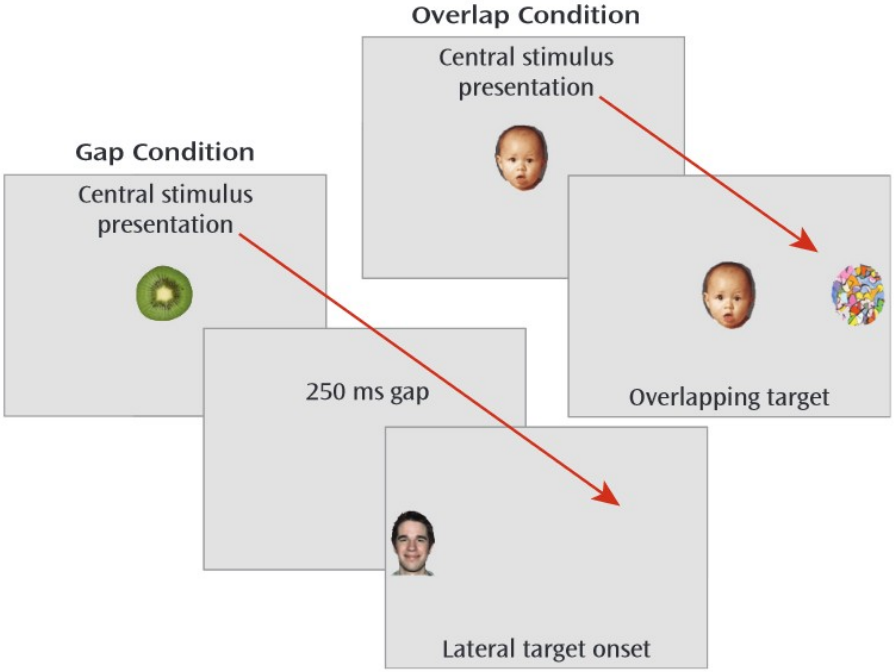
- EU-AIMS task
- Central fixation on black background flashes white for 75ms
  - Interspersed video clips induce saccades
- Discriminates
  - ASD vs. TD in infants,

  Children, and adults



ET: Gap overlap task

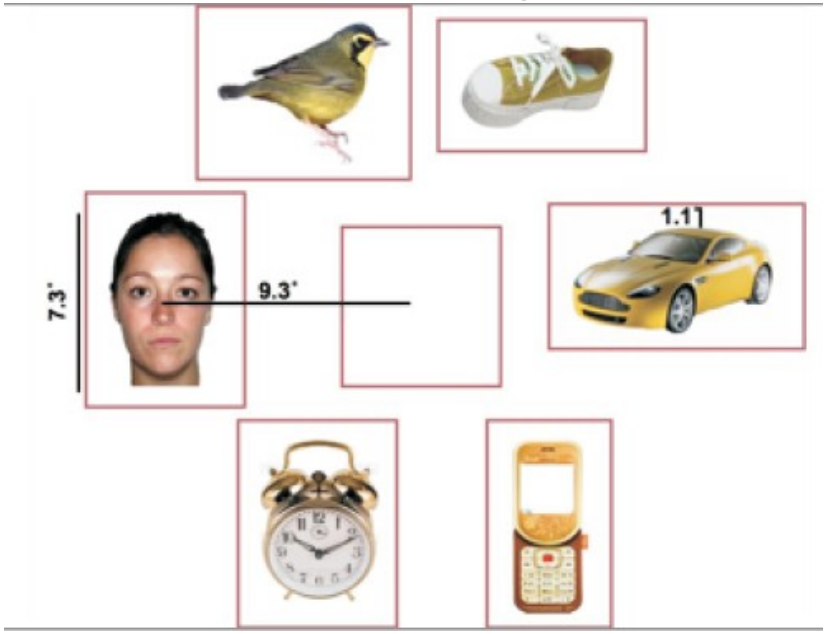
- EU-AIMS task
- Attention shifting and flexibility



- Discriminates ASD vs. TD in infants, children, adults

ET: Visual search/Static images

- EU-AIMS task
- Salience of social stimuli among distracters

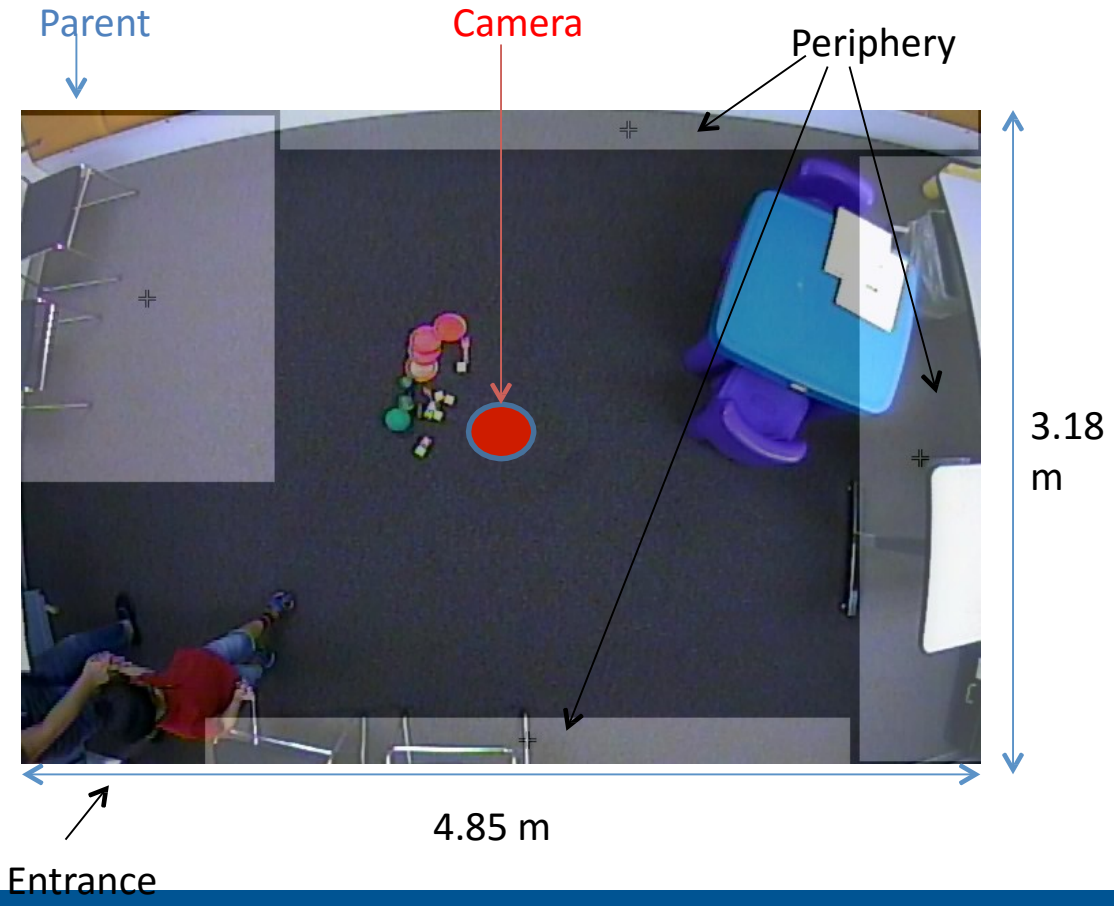


- Discriminates ASD vs. TD in children

Lab-based Measures

Lab-based measures: Video Tracking

- Proximity seeking during free play



Lab-based measures: Video Tracking

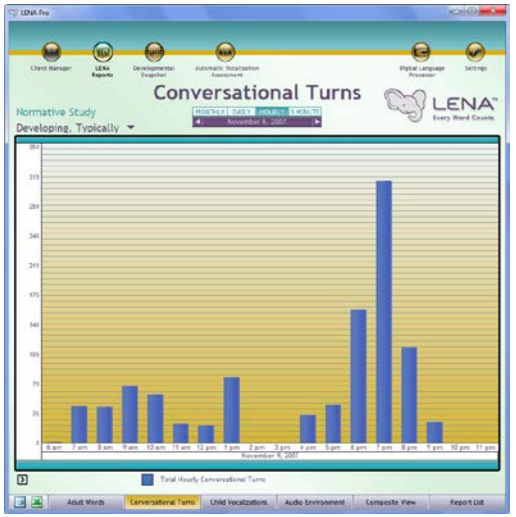
PARENT TD

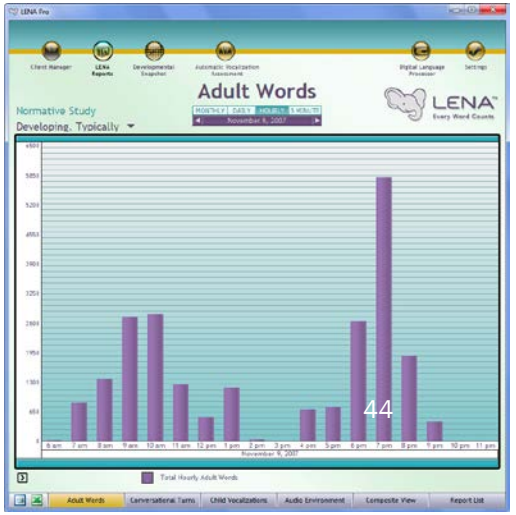
PARENT ASD

- Social avoidance correlates with social-communicative impairment

Lab-based measures: LENA

- Language ENvironment Analysis
  - Conversational turns
  - Vocalizations
- Data collected in lab and at home
- Associated with social communicative function in Duke clinical trial





Lab-based measures: Face and affect recognition

- Affect recognition
  - NEPSY-II
    - Administer to all
    - Normed 3-11
- Face recognition
  - Kaufman Assessment Battery for Children
    - Administer to age 4
    - Normed 3-6
  - NEPSY-II
    - Administer to all
    - Normed 5-11

Clinician/caregiver assessments

- **Clinician administered**
  - Autism Diagnostic Observation Schedule
  - Autism Diagnostic Interview – Revised
  - Vineland Adaptive Behavior Scales
  - Differential Ability Scales
  - Clinical Global Impression Scale

- **Caregiver report**
  - Aberrant Behavior Checklist
  - Autism Impact Measure
  - Behavior Assessment System for Children – Second Edition
  - Pervasive Developmental Disorder Behavior Inventory
  - Social Opportunities Questionnaire
  - Social Skills Improvement System
  - Social Responsiveness Scale – Second Edition
  - Child and Adolescent Symptom Inventory
  - Pediatric Quality of Life
  - Caregiver Strain Questionnaire
  - ACE Family/Medical History
  - Intervention History
  - Demographics/Screening

Biospecimens

- Blood draw
  - Proband and available biological parent(s)
  - Simons Foundation SPARK
    - 1 EDTA for DNA extraction and sequencing
  - NIMH Repository
    - 1 LCL/ACD tube for generation of cell lines
    - 1 EDTA
- Genetic feedback to families via SPARK

Planned Interim and Final Data Analyses

- Assess technical and biological viability of the measures as potential biomarkers:
  - Identify EEG and eye tracking biomarkers and lab-based measurement variables with good performance metrics
  - Examine the relationship and sensitivity among EEG and eye tracking biomarkers, lab-based measures, clinician/caregiver assessments, and independent measures of clinical status
  - Evaluate longitudinal change in eye tracking, EEG, and lab-based measures to identify if they will be sensitive tools for intervention trials

- Use multivariate methods to find meaningful groups of individuals or variables
  - Cluster analysis to identify homogenous subgroups based on these variables and check for their correspondence with known/observed patterns of heterogeneity in ASD symptoms and behaviors
  - Multidimensional scaling to identify composites by capturing heterogeneity in the sample across measures

Expected Outcomes

- The ABC-CT is an early stage biomarker validation effort
  - Determine if biomarkers are robust enough to be used for subject selection of school-aged ASD subjects for clinical trials
  - Assess technical and biological variability of the measures in pre-
    - school and school-aged children
  - Assess the utility of investigator-administered assessments of domains of social impairment as predictors of clinical outcomes
- A public data resource
  - An integrated data set of EEG, eye tracking, lab-based, and clinical
    - measures from pre-school and school-age ASD subjects, as well as
    - blood samples from ASD subjects and their parents for future genomic analyses
  - All data and analyses made publicly available through the National
    - Database for Autism Research

Status and timeline

- Current status
  - Complete
    - Protocol review by External Advisory Board
    - In-person protocol finalization meeting with SC and BCPT
    - Experimental paradigms and clinical protocols
    - Hardware configuration and standardization
    - Study-wide and site-specific trainings
    - Electronic case report forms and data management infrastructure
    - Site visits by DCC and DAAC
  - Feasibility study enrollment commenced December 8
  - Feasibility analyses ongoing
  - Three month goal for feasibility study completion
    - Presentation to Biomarkers Consortium Executive Committee
- Timeline
  - Three year data collection period
  - Finalization of analyses and publication in Year 4

Meeting of the IACC

Morning Agenda

10:15 AM **National-Level Outcomes of Transition-Age Youth on the Autism Spectrum**

Anne Roux, M.P.H., M.A.
Research Scientist,
A.J. Drexel Autism Institute

11:00 **Break**

National-level outcomes of transition-age youth on the autism spectrum

Anne M. Roux, MPH, MA

Life Course Outcomes
Research Program

DREXEL UNIVERSITY
A.J. Drexel
Autism Institute

This project was supported by the Health Resources and Services Administration (HRSA) of the U,S, Department of Health and Human Services under grant number, UA6MC27364, and title, **Health Care Transitions Research Network for Youth and Young Adults with Autism Spectrum Disorders** for the grant amount of $900,000. The information or content and conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS, or the U.S. government.

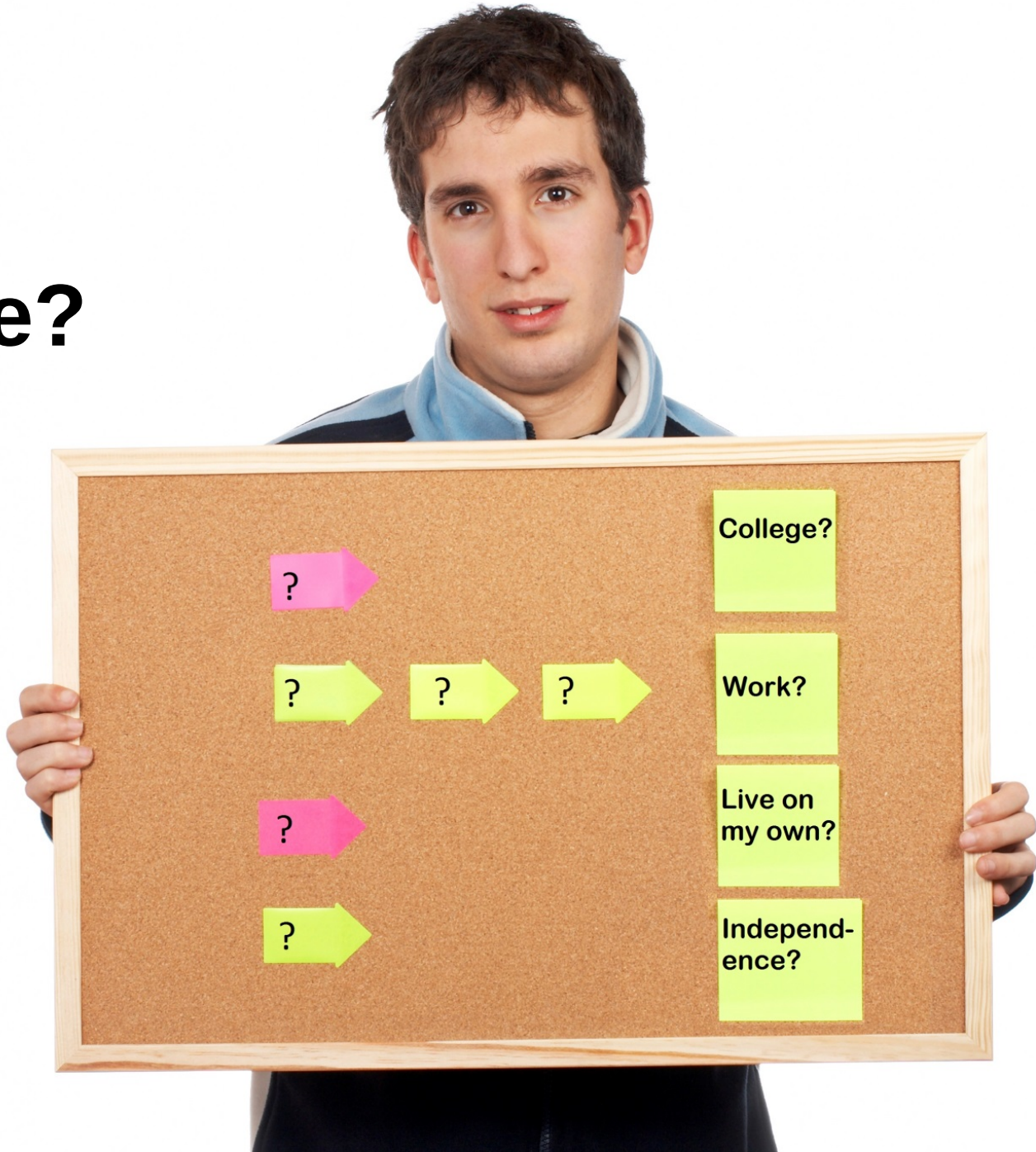
A public health approach to autism

Primary	Secondary	Tertiary
Reduce/eliminate avoidable causes	Identify symptoms early and intervene	Minimize disability and promote quality of life
Modifiable Risk Factors	**Early Detection & Intervention**	**Life Course Outcomes**
Craig Newschaffer, Ph.D.	**Diana Robins, Ph.D.**	**Paul Shattuck, Ph.D.**

50-70,000 children with autism turn 18 and enter the adult service system every year.

-Shattuck, Roux, et al 2012

What is a life course perspective?




National Autism Indicators Report
Transition into Young Adulthood
2015

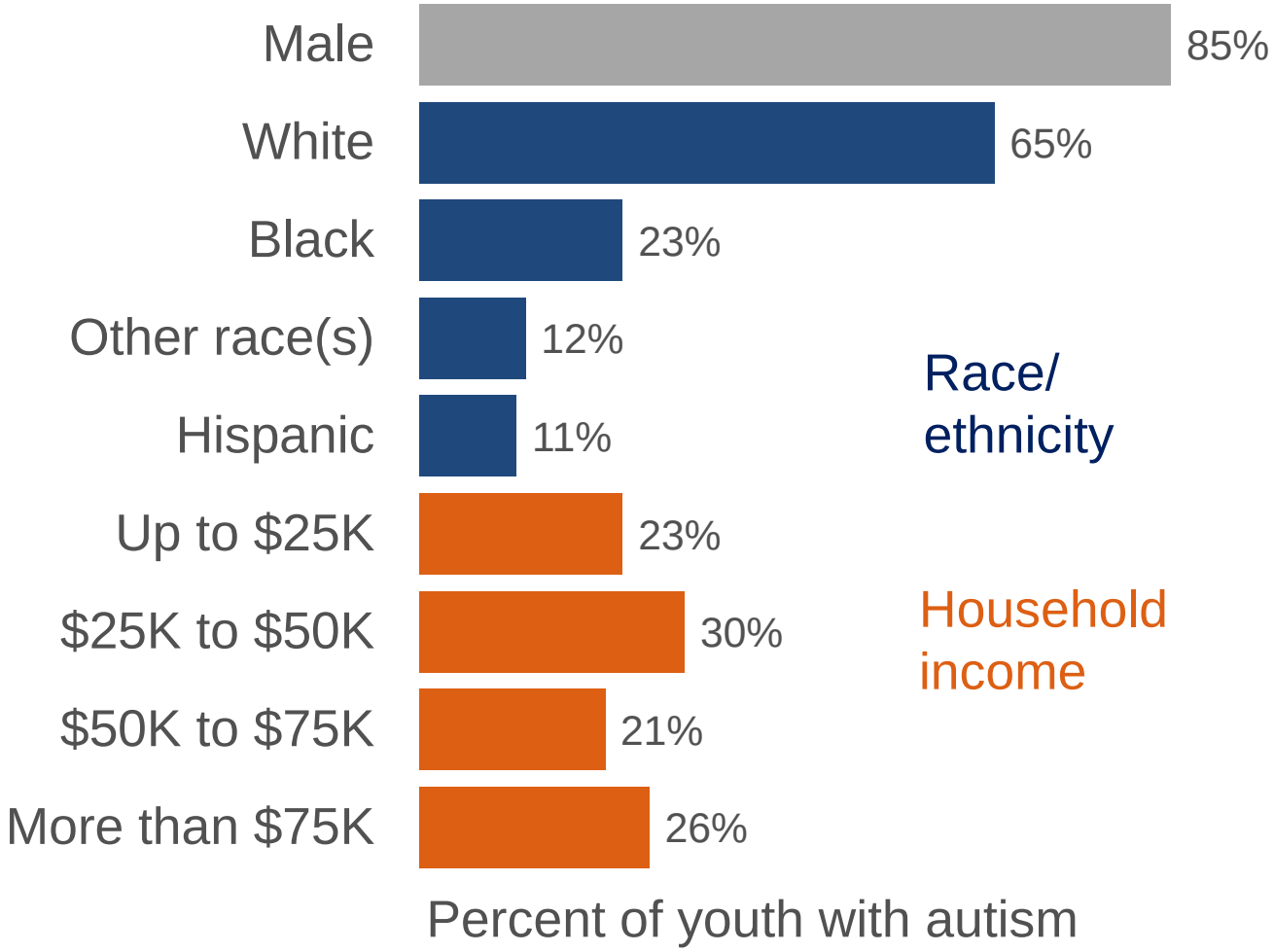
Data Sources

- National Longitudinal Transition Survey 2 (NLTS-2)
- Survey of Pathways to Diagnosis and Services

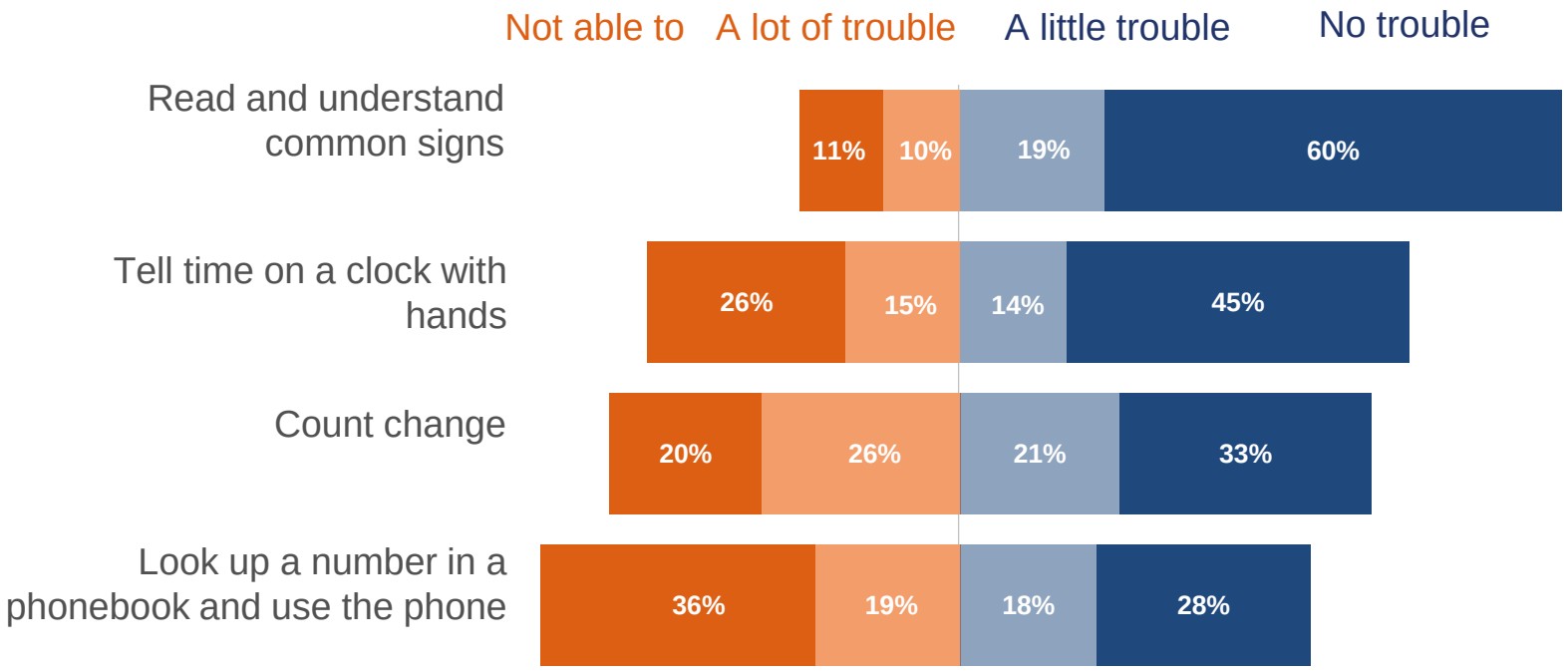
Outcome domains

What were the characteristics of youth at the time of transition?

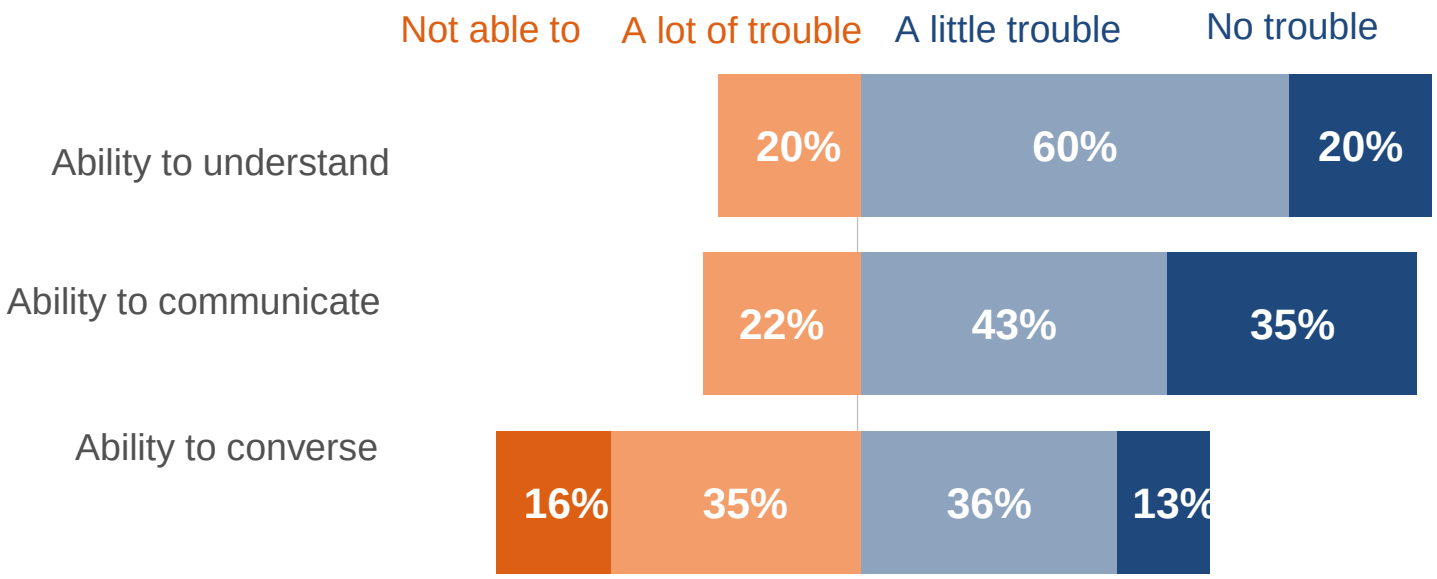
Autism Demographics



Ability to perform activities of daily living varied.

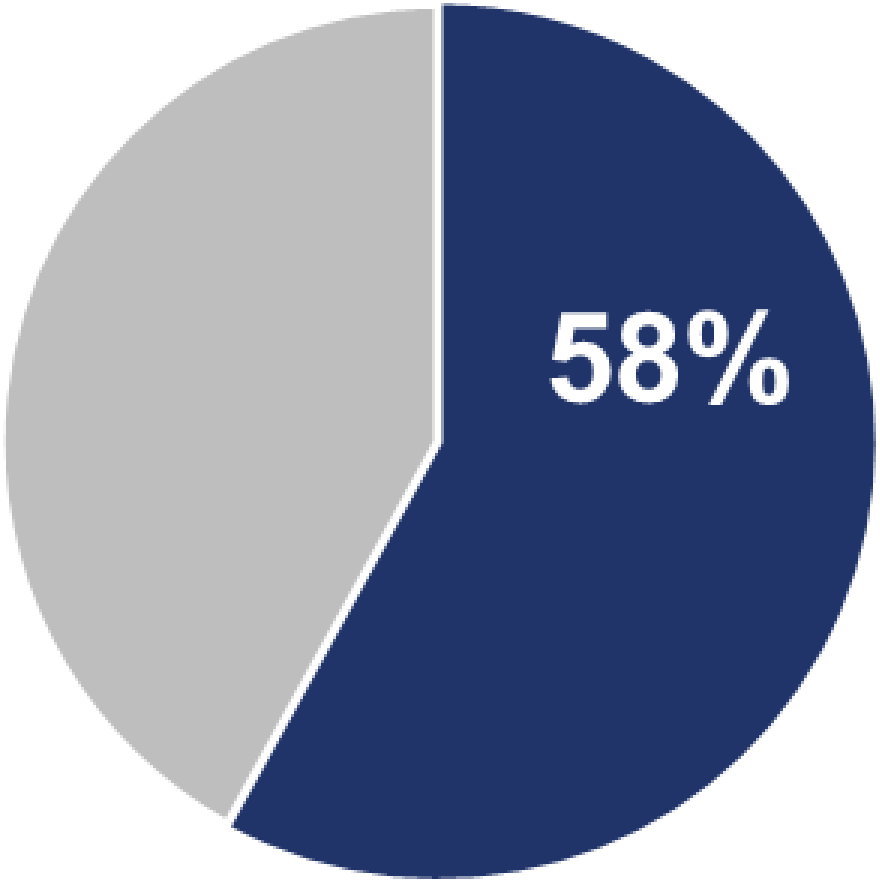


Over half had great difficulty conversing.



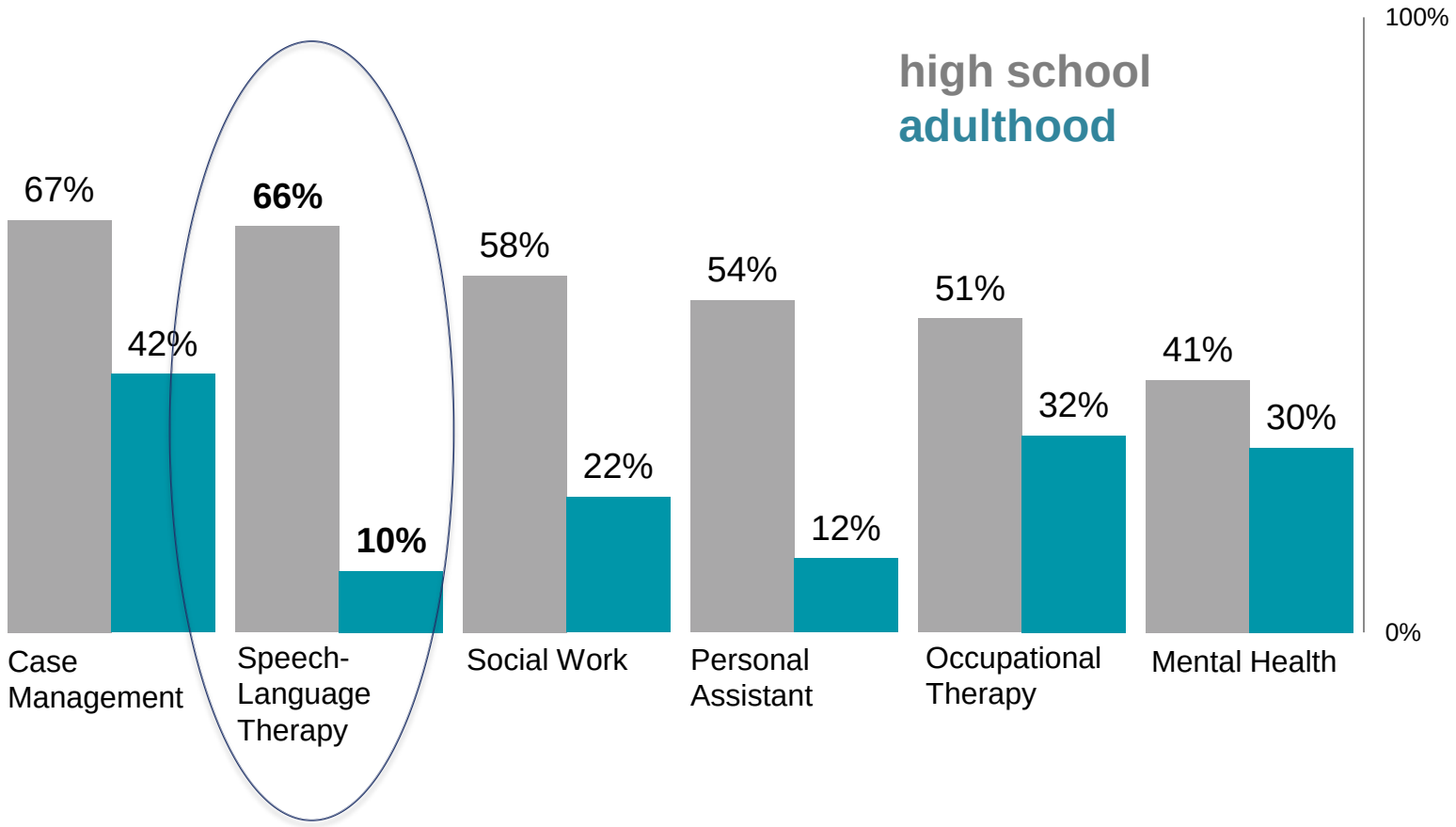
What supports did youth with autism receive as they entered adulthood?

Inconsistent receipt of transition planning



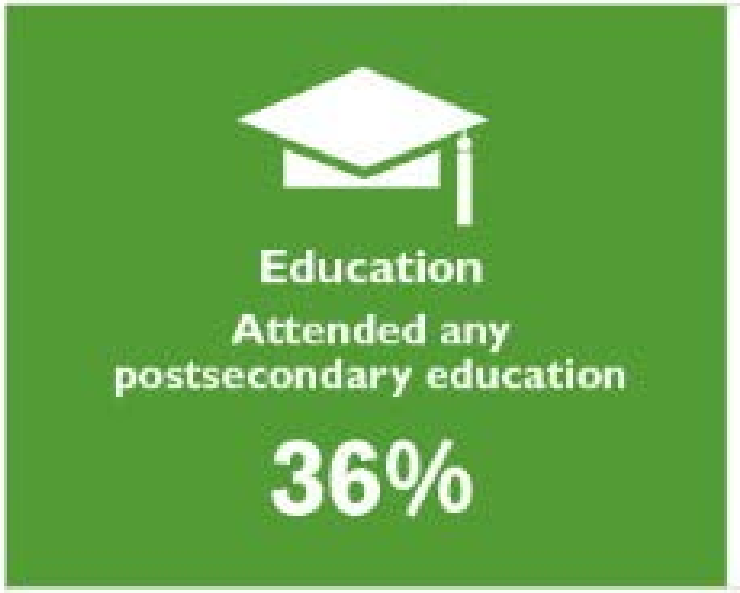
of youth with autism had a transition plan by the required age according to their teachers.

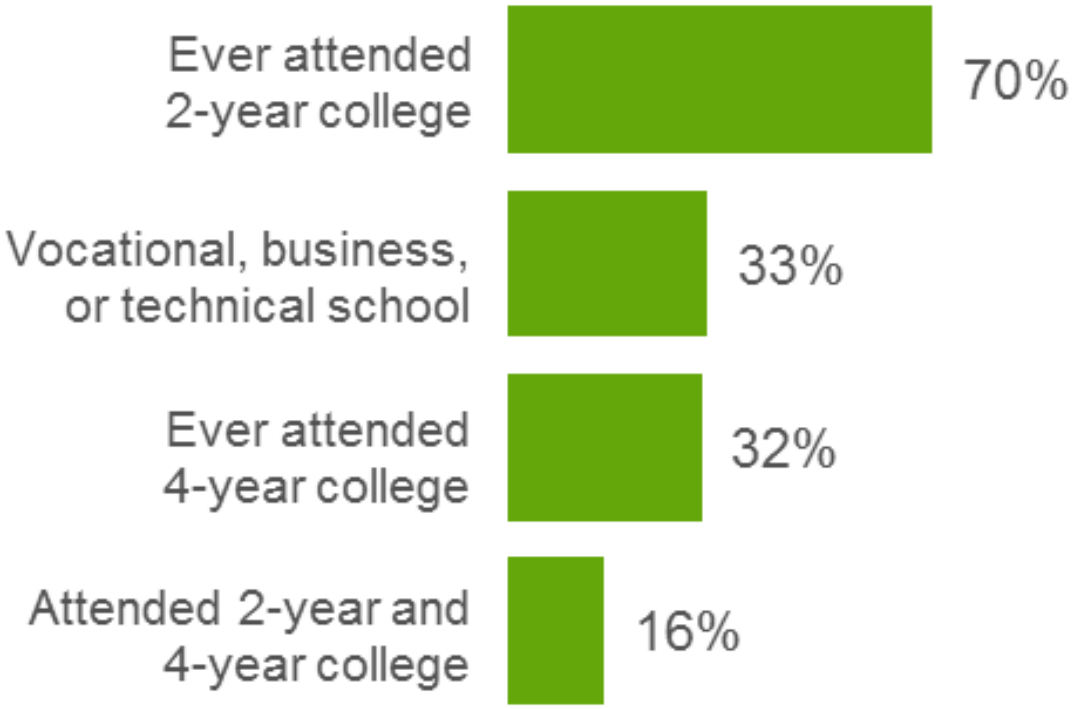
The services cliff



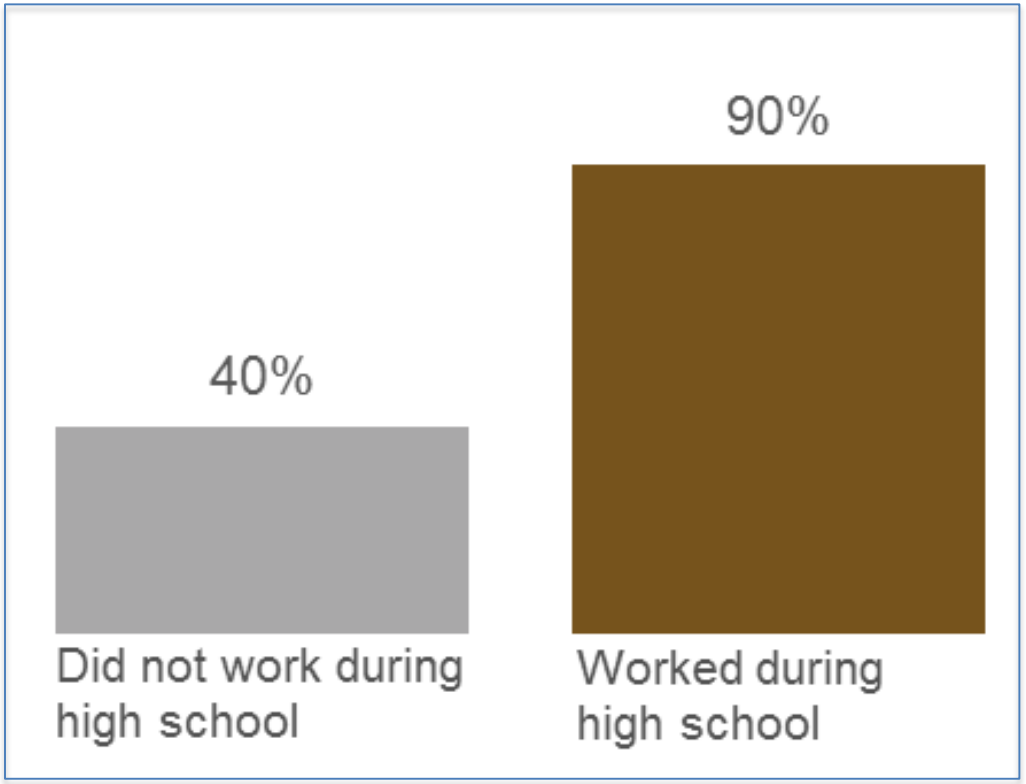
What happened to transition-age youth with autism between high school and their early 20s?

One-third ever attended post-secondary education.

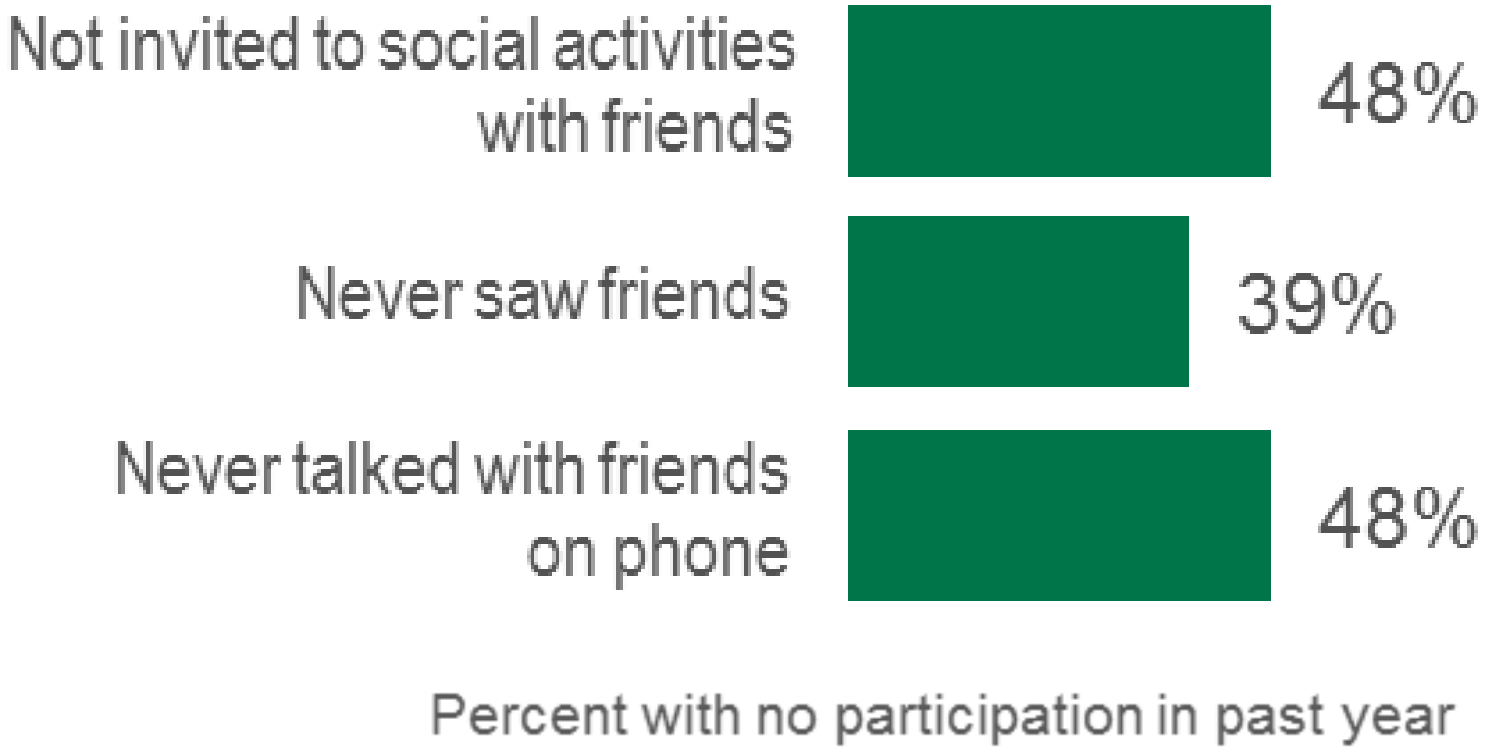




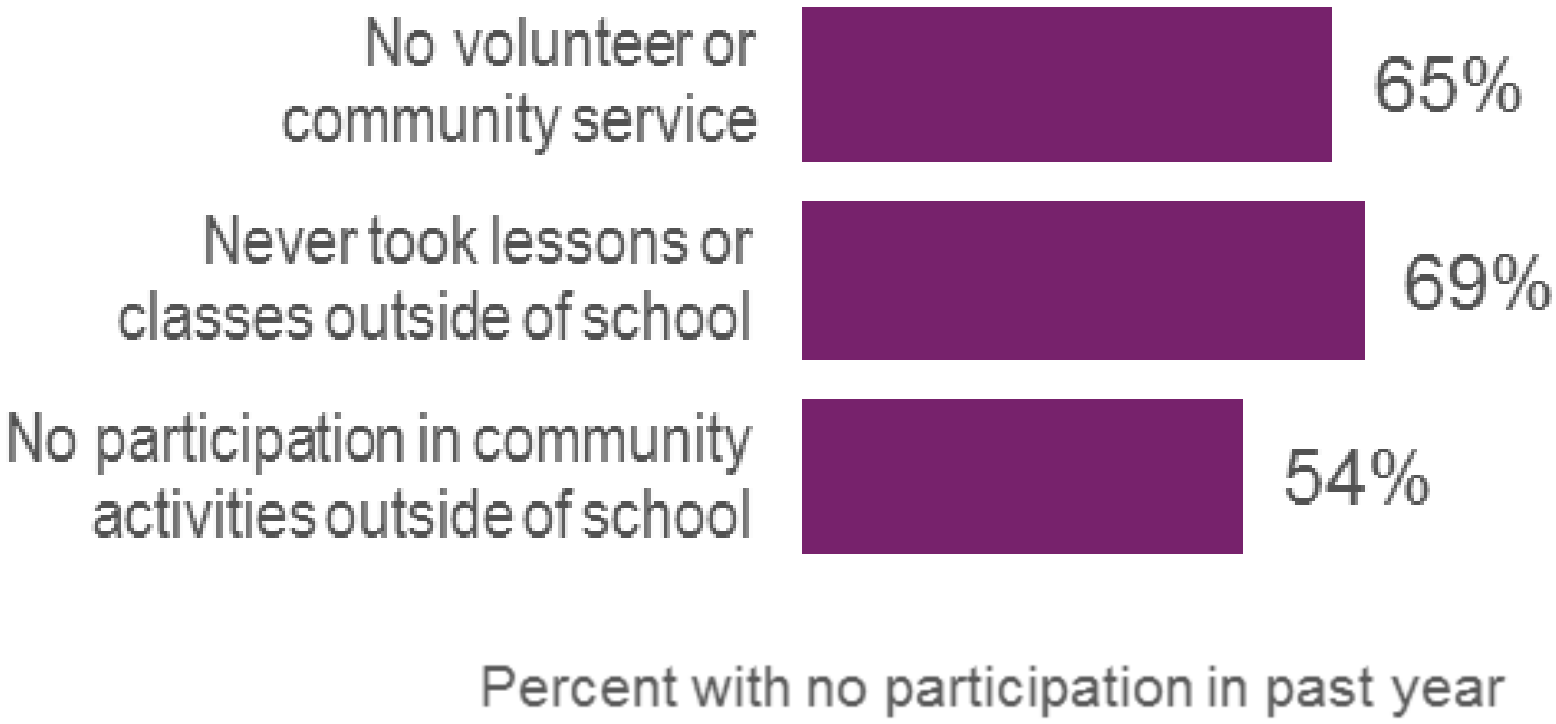
Half ever held a job.



One-quarter were socially isolated.



One-third had no community participation.



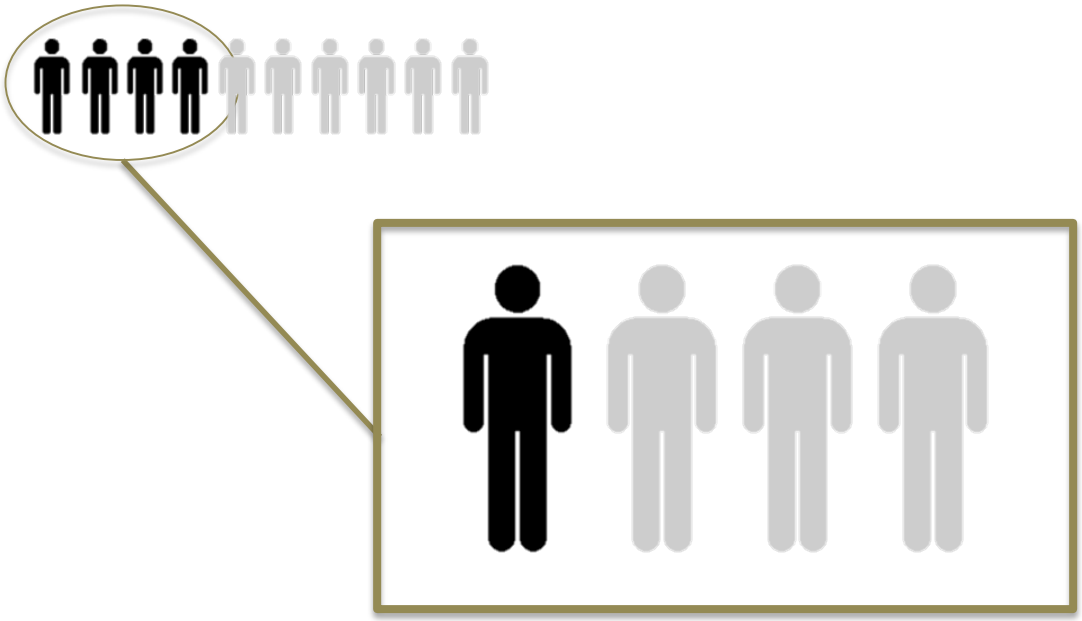
Postsecondary Connection

Employment

College

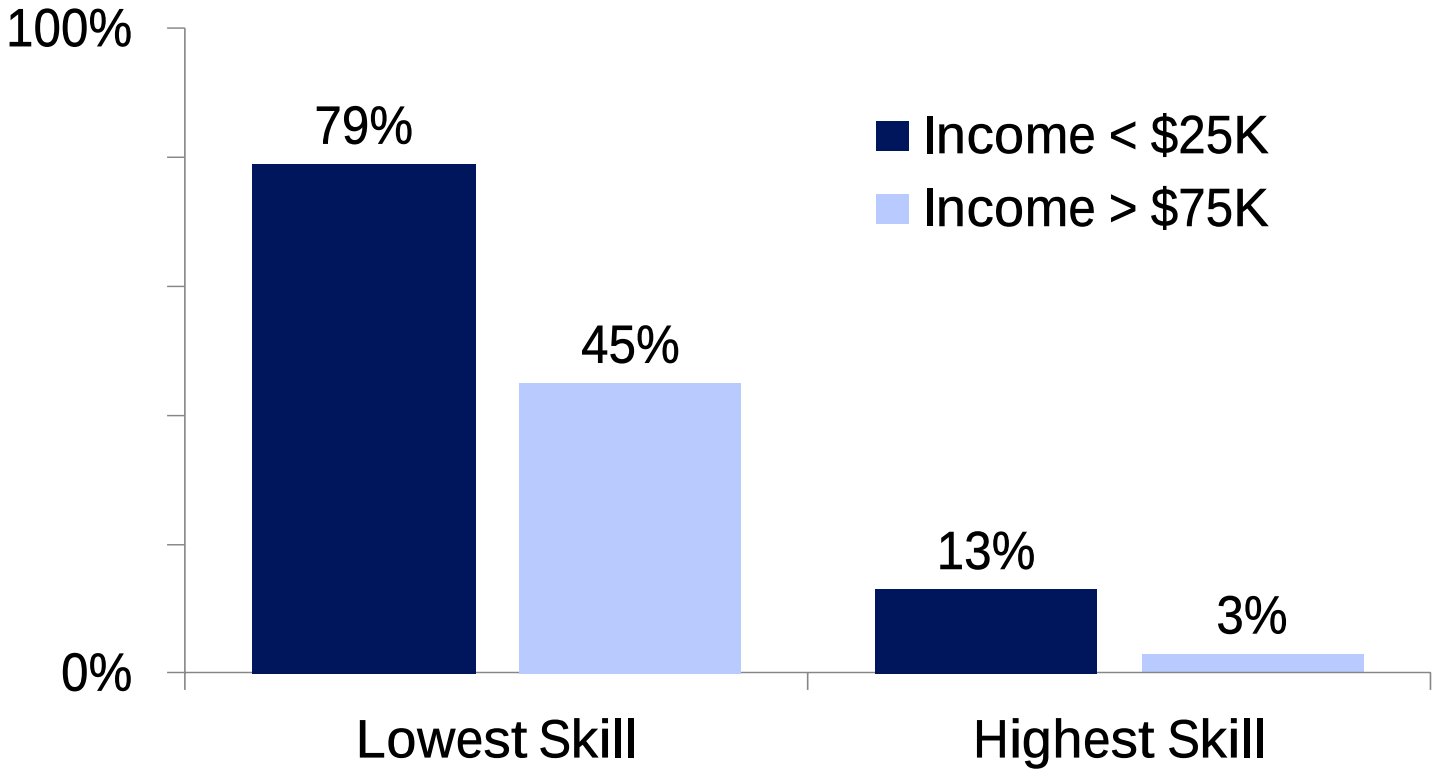
Voc/tech school

Four in 10 were completely **disconnected** from both work and continued education opportunities.



One in four disconnected young adults had **no access to services** since high school.

Disconnection levels are high in those with lower level skills and lower income.

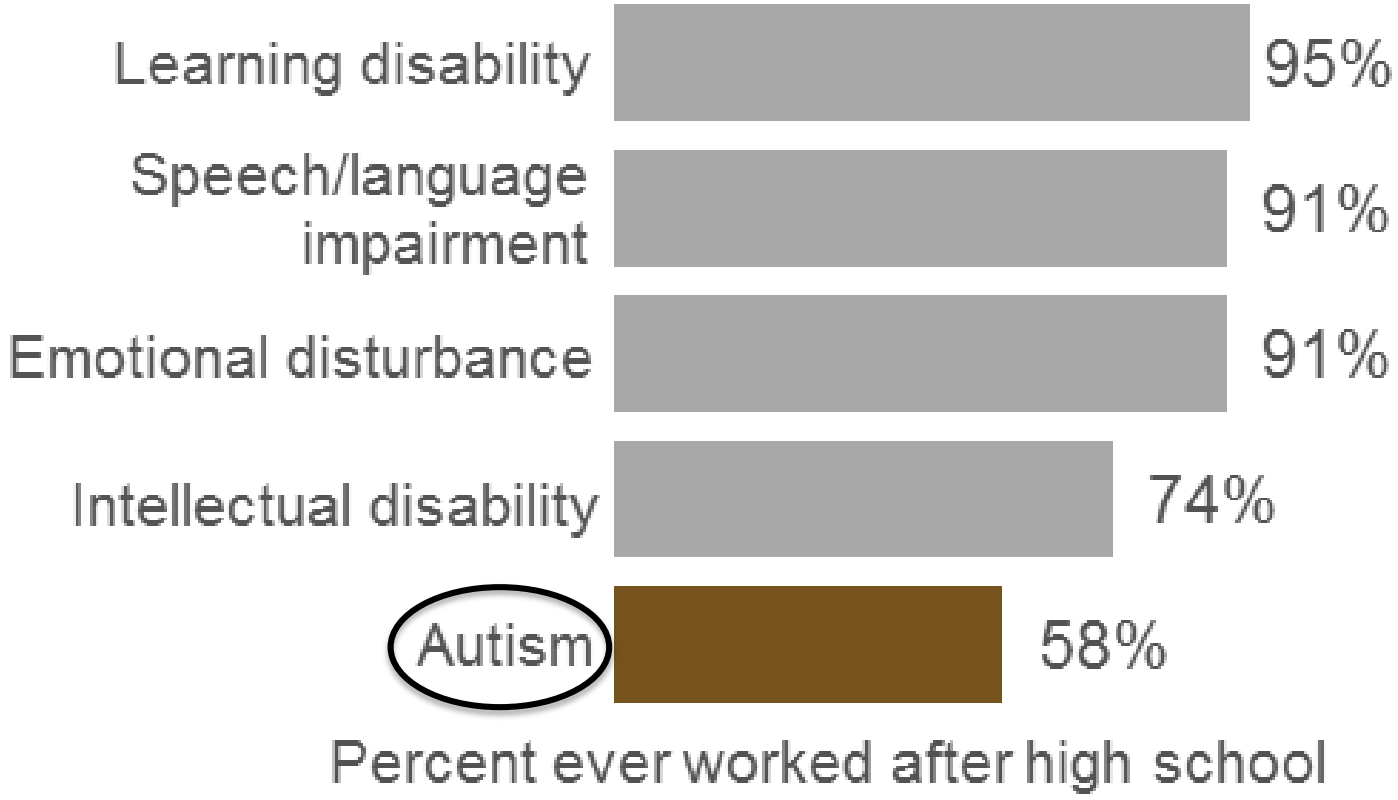


Shattuck et al, 2012. *Pediatrics* 129(6).

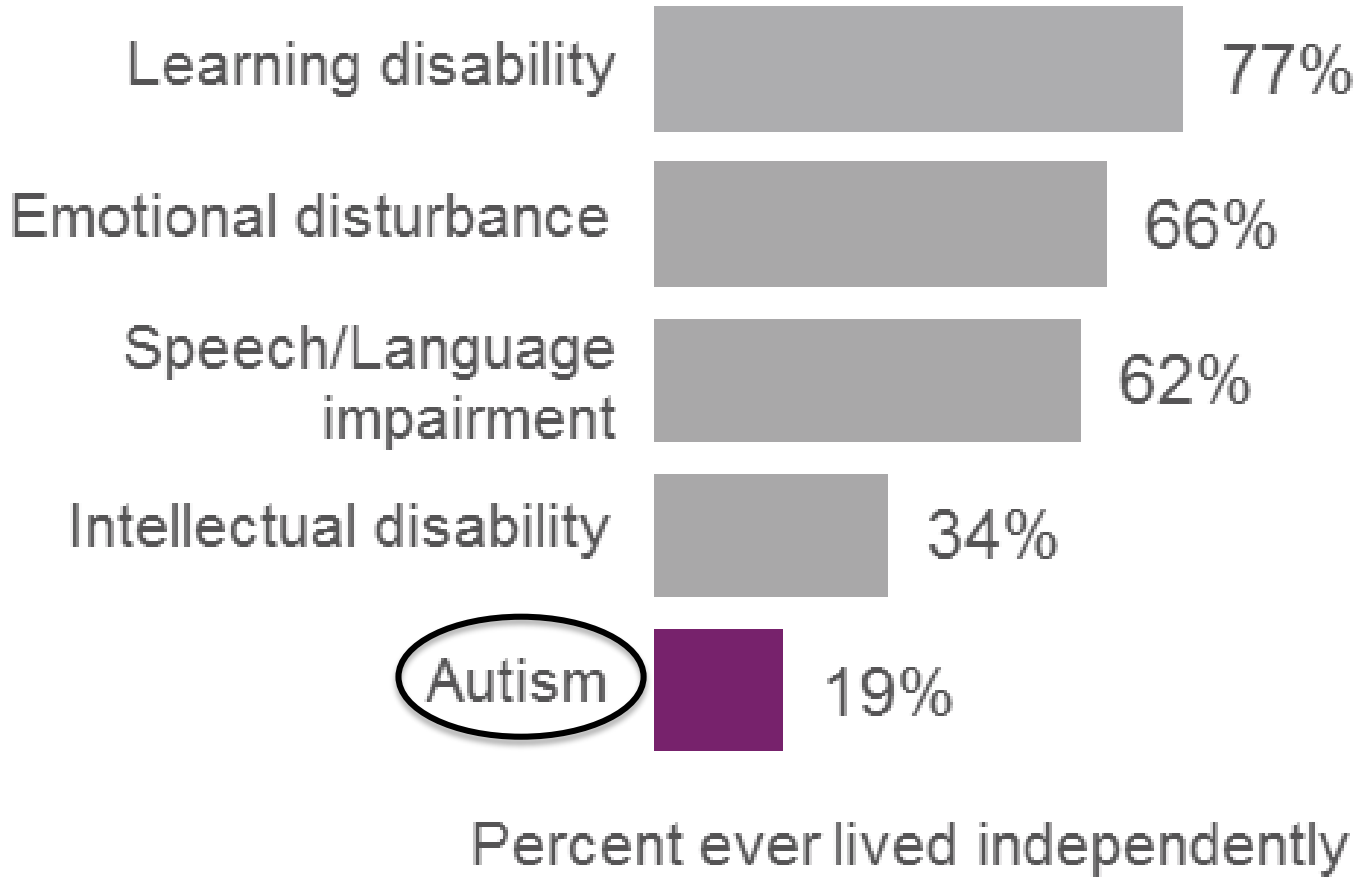
Insights from the NLTS2

Young adults with autism fared worse relative to those with other disabilities.

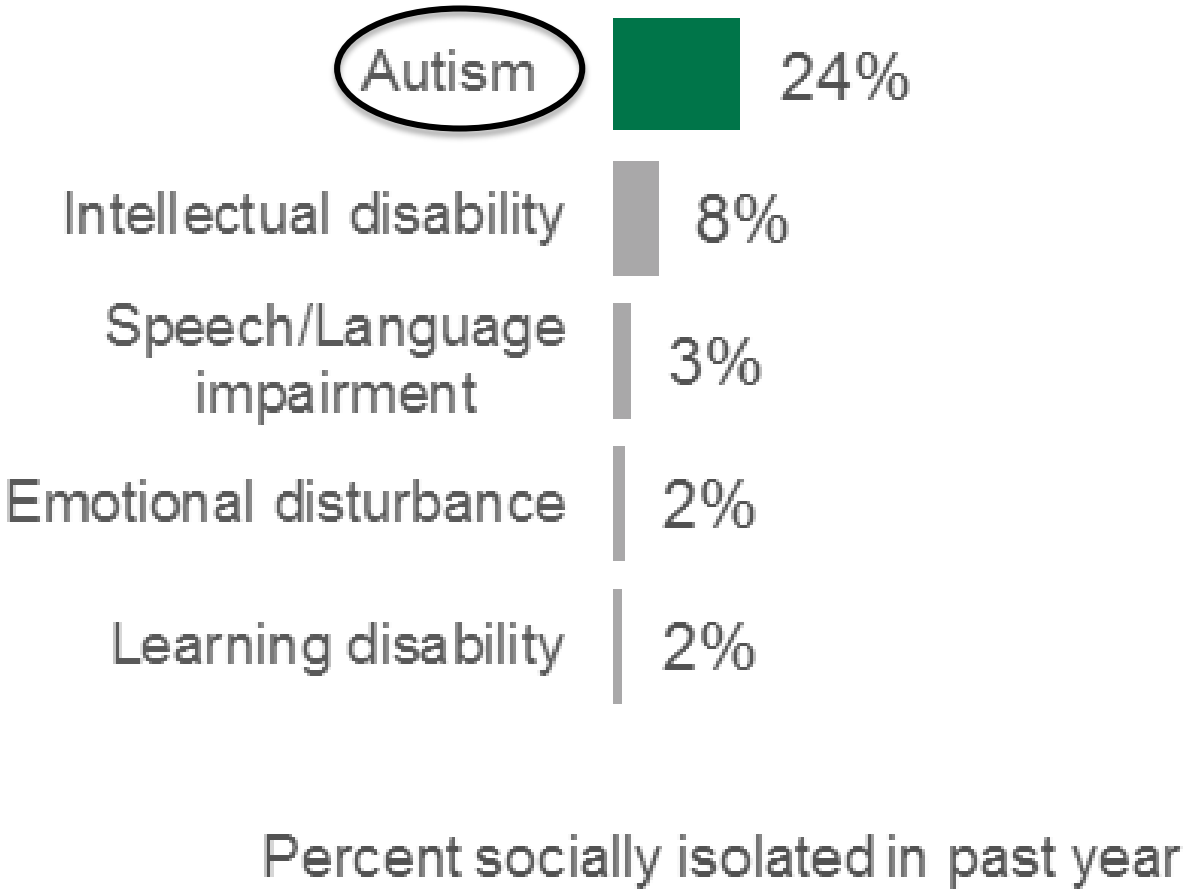
Rates of employment



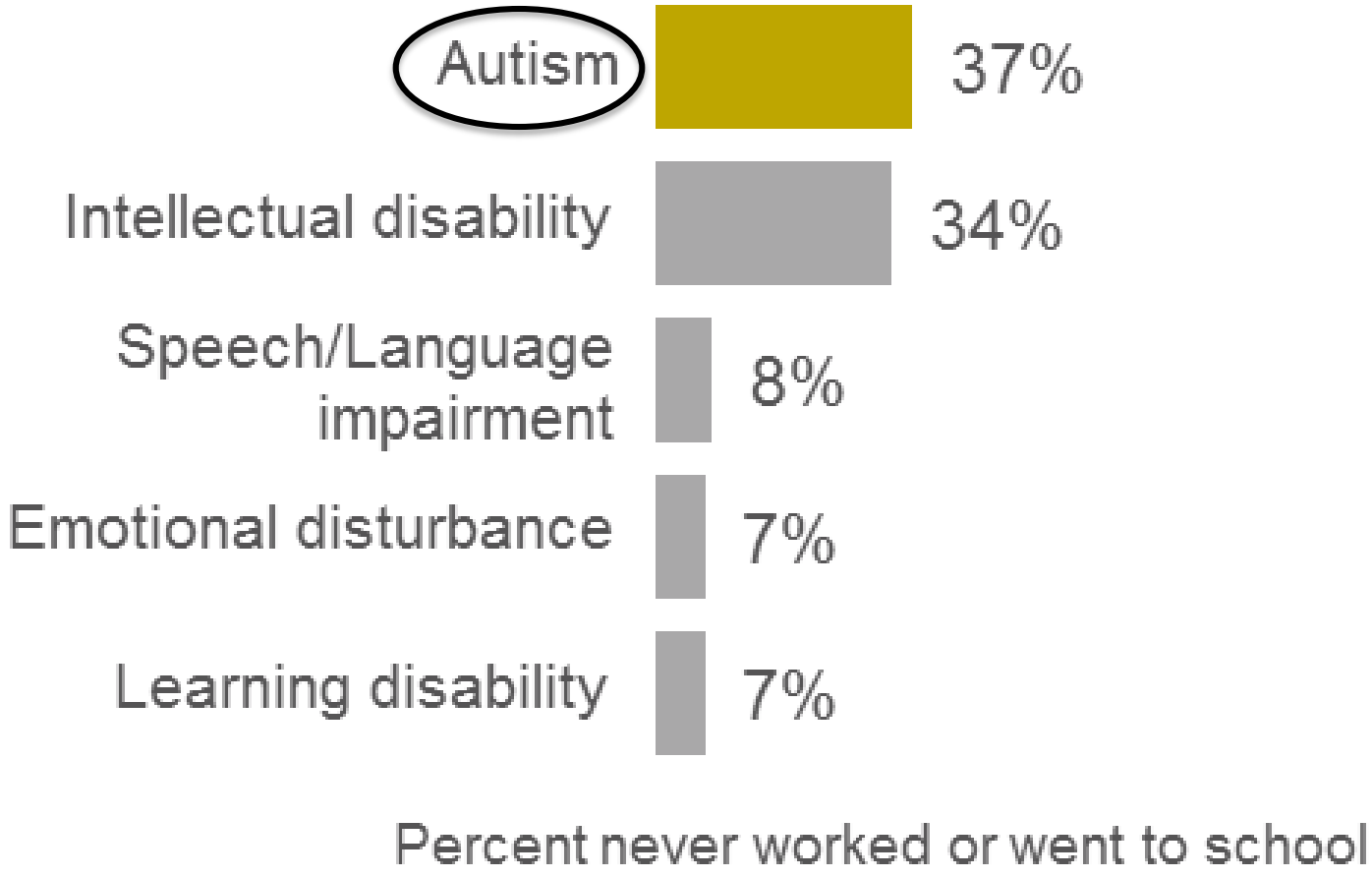
Rates of independent living



Rates of social isolation



Rates of disconnection



Results

- Congressional autism caucus briefing
- Consultation with the U.S. Government Accountability Office
- NPR On Point interview
- NPR Diane Rheme show
- 7 additional media interviews
- 4 invitations for national conference presentations
- Drexel top news events of 2015

DREXEL UNIVERSITY
Life Course Outcomes
Research Program
A.J. Drexel Autism Institute

TOPICS | PUBLICATIONS AND REPORTS | PROJECTS | NEWS | BLOG | ABOUT

EXPLORE OUR RESEARCH

Learn about major projects currently underway, and where our research is headed.

BETTER RESEARCH MEANS BETTER OUTCOMES

How can we improve the lives of people on the autism spectrum? This is the big question we at the Life Course Outcomes team are working to answer. Our award winning research informs policy and services at the community and national levels on ways to improve quality of life.

We cover a wide range of topics, all related to producing better life outcomes for people on the autism spectrum.

- TRANSITION TO ADULTHOOD
- ACCESS TO SERVICES
- EDUCATION
- EMPLOYMENT

NOTABLE PUBLICATIONS

NATIONAL AUTISM INDICATORS REPORT: TRANSITION INTO YOUNG ADULTHOOD
An in-depth report on outcomes of young adults with autism following high school

INVOLVEMENT IN THE CRIMINAL JUSTICE SYSTEM AMONG YOUNG ADULTS ON THE AUTISM SPECTRUM
Individuals with autism may be at risk for criminal justice involvement due to differences in social communication skills and behavioral characteristics.

Life Course Outcomes
Research Program

DREXEL UNIVERSITY
A.J. Drexel
Autism Institute

Looking ahead

Paramount needs:

- Population health research
- Funding for secondary data analysis
- Purposeful planning of data collection
- Longitudinal study

National Autism Indicators Report:

Vocational Rehabilitation

2016

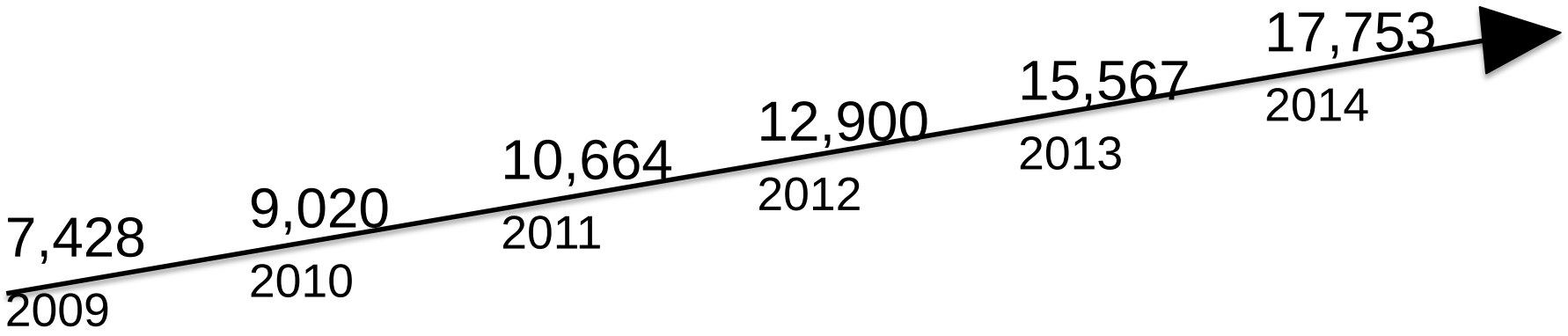
Life Course Outcomes
Research Program

Drexel University
A.J. Drexel
Autism Institute

VR and Autism

Preliminary numbers

- Nearly 18,000 applicants with autism exited vocational rehabilitation in 2014.



VR and Autism

Preliminary numbers

- Approximately 1/3 of those who applied did not receive services.
- 60% of VR participants with autism exited with employment
- Age is an important factor in employment outcomes for this group.

What we would like to know

- Size of the population who needs VR help
- Reasons families do not apply for VR help
- Reasons for not receiving services
- Why some states have better outcomes
- What works or does not works about VR
- Job placement satisfaction and match
- Movement in/out of VR over time
- Changes in need for public benefits

Information & Acknowledgments

A.J. Drexel Autism Institute's
Life Course Outcomes Research Program
www.drexel.edu/AutismOutcomes

National Autism Indicators Report
drexe.lu/autismindicators

- Paul Shattuck, PhD, MSSW, Program Director
- Anne Roux, MPH, MA, Lead Author and Producer
- Jessica Rast, MPH, Data Analyst
- Julianna Rava, MPH, Research Assistant
- Kristy Anderson, MSW, Research Associate

Meeting of the IACC

Break

Meeting of the IACC

Morning Agenda

11:15 AM **Committee Business**

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

Bruce Cuthbert, Ph.D.
Acting Director, NIMH and Chair, IACC

- **IACC Strategic Plan Update**
- **IACC Summary of Advances**

12:15 PM **Lunch**

IACC Committee Business

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

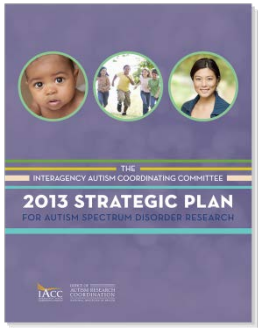
IACC Full Committee Meeting
January 12, 2015

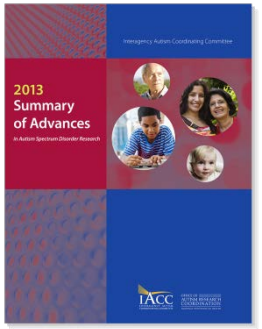
These slides do not reflect decisions of the IACC and are for discussion purposes only.

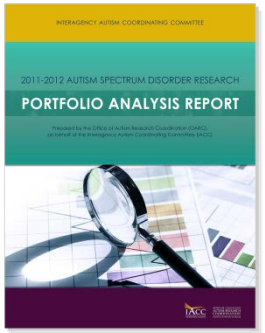
.

IACC Responsibilities

- Develop and annually update a strategic plan for ASD
- Develop and annually update a summary of advances in ASD research
- Monitor Federal activities with respect to ASD
- Make recommendations to the HHS Secretary regarding research or public participation in decisions regarding ASD



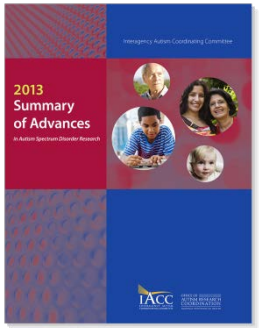




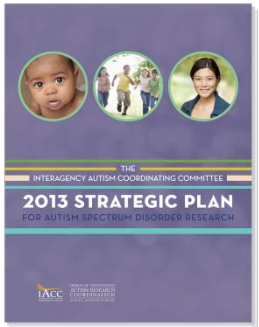
These slides do not reflect decisions of the IACC and are for discussion purposes only.

Immediate To-Do List

- Develop two volumes of the IACC Summary of Advances in ASD Research (2014 and 2015)



- Develop an update of the IACC Strategic Plan (2016 Update) that will cover progress made in 2014 and 2015



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

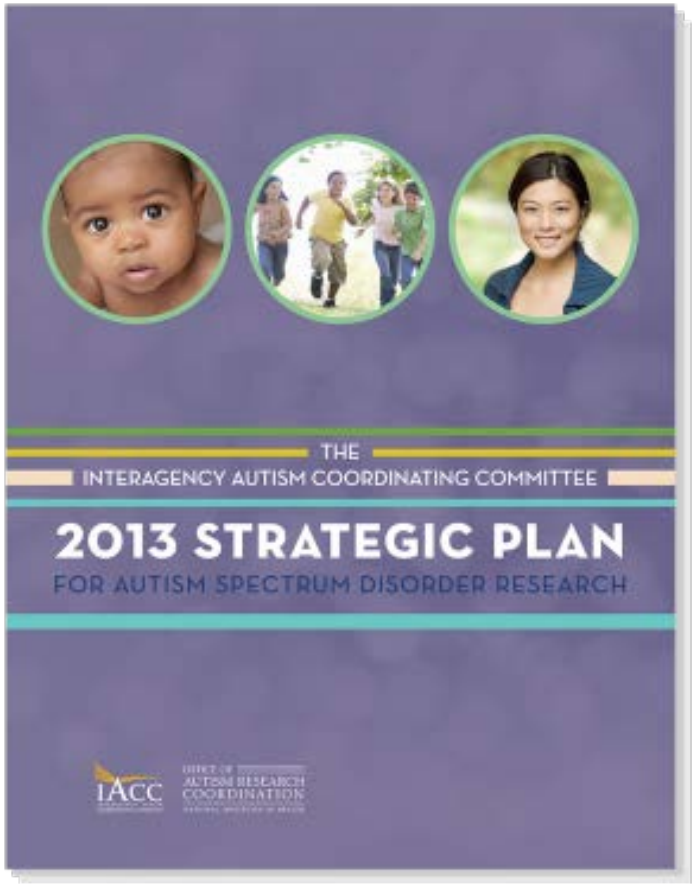
Summary of Advances Update

The committee decided to use the same process as previous years to develop the Summary of Advances:

- OARC provides and committee nominates peer reviewed research publications – Process started
- Committee will select up to 20 advances under each of the 7 areas of the Strategic Plan
- OARC will write short, lay-friendly summaries of the selected articles
- The 20 advances from each year are each combined into a booklet format – 2 booklets
- Final documents will be completed in 2016
- Will provide an update in April 2016

IACC Strategic Plan Update

Finalize plans for the next IACC Strategic Plan Update



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

Autism CARES Act and the IACC SP

The Autism Collaboration, Accountability, Research, Education and Support Act (P.L. 113-157):

- Continues to require the IACC to prepare an annual update of the IACC Strategic Plan
- Requires that the IACC Strategic Plan continue to address research, but also include as practicable, services and supports for individuals with ASD and their families as well as recommendations to ensure that federal ASD research and services activities are not unnecessarily duplicative:
- The IACC shall **"develop a strategic plan for the conduct of, and support for, autism spectrum disorder research, including as practicable for services and supports…"**

Autism CARES Act (continued)

The Autism Collaboration, Accountability, Research, Education and Support Act (P.L. 113-157):

- The strategic plan, **"shall include proposed budgetary requirements and recommendations to ensure that autism spectrum disorder research, and services and support activities to the extent practicable, of the Department of Health and Human Services and of other Federal departments and agencies are not unneccessarily duplicative."**

- Requires that the IACC Strategic Plan be submitted to Congress and the President

Structure of IACC Strategic Plan

Framed around 7 consumer-based Questions:

- Question 1: When Should I Be Concerned?
- Question 2: How Can I Understand What Is Happening?
- Question 3: What Caused This to Happen and Can It Be Prevented?
- Question 4: Which Treatments and Interventions Will Help?
- Question 5: Where Can I Turn for Services?
- Question 6: What Does the Future Hold, Particularly for Adults?
- Question 7: What Other Infrastructure and Surveillance Needs Must Be Met?

Structure of IACC Strategic Plan

Each Question has:

- An **Aspirational Goal**, describing long term goals for the field and outcomes for individuals on the autism spectrum
- **Introduction** (**What do we know? What do we need?**) that provides background on the field and needs pertaining to that question.
- **Progress toward the SP Objectives** – a summary
- **Progress in the field** – describing recent research advances
- **Progress toward the Aspirational Goal**
- **Research Objectives** (if any new)

2016 Strategic Plan Update – Option 1 Encompassing Both Research and Services

- **Each of 7 Questions addresses both research and services issues related to the question**
- **Aspirational Goal**, describing long term goals for the field and outcomes for individuals on the autism spectrum
- **Introduction** (**What do we know? What do we need?**) that provides background on the field and needs pertaining to that question – addressing both research and services
- **Progress toward the SP Objectives** – summarize progress made on previous SP objectives to understand state of funding for all areas of SP

2016 Strategic Plan Update – Option 1 Encompassing Both Research and Services

- **Progress in the field** – Split into 3 sections:
  - Advances in Research
  - Innovation in Services
  - Changes in Policy
- **Progress toward the Aspirational Goal**
- **Future Directions** - Address remaining gaps and issues related to ensuring the translation of research to services and benefits, and feedback from services experience to enhance research
- **Develop new 2016 Research and Services Objectives**
- Rename the SP the "**IACC Strategic Plan for ASD"**

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

2016 Strategic Plan Update – Option 2 Separate Research and Services Plans

- Keep current research Strategic Plan and structure, but develop a new set of research objectives
- Develop a separate Services Plan, with a structure TBD

Objectives for the 2016 IACC SP

- Most of the current 78 SP objectives date to 2011 and have been accomplished or are in progress
- Is it time for a new/revised set of objectives? (research and services?)
- If so, how many, or how many per Question?
- Should the format of objectives be similar to current or less specific?

Objectives for the 2016 SP Update (Cont'd)

- **Example of current SP Objective:**

  1SA. Develop, with existing tools, at least one efficient diagnostic instrument (i.e., briefer, less time intensive) that is valid in diverse populations for use in large-scale studies by 2011. IACC Recommended Budget: $5,300,000 over 2 years.

- Do we need to designate objectives as long term and short term? Was it helpful?
- Do we want specific deadlines tailored to each objective, or have most/all objectives share a common deadline (e.g. 2019 [3yr] or 2021 [5yr])?
- Current objectives are very specific – do we want new objectives to be more inclusive/higher level?

Planning the SP Update

Whether Option 1 or Option 2 chosen:

- Start with 7 working groups for the 7 Questions of the SP/research SP. Membership flexible.
- Does the committee want to invite external experts to participate? If so, perhaps 3-6 per WG?
- Structure a series of phone meetings for each WG – 3 meetings to cover the sections of the SP Update.
- Do we need an in-person workshop to discuss draft document among whole group after initial drafts completed?

Planning the SP Update (cont'd)

- Each group will be provided with data from the 2013 Portfolio Analysis to review research funding – summary data and grant lists
- IACC required to provide "recommendations to ensure that autism spectrum disorder research, and services and support activities to the extent practicable, of the Department of Health and Human Services and of other Federal departments and agencies are not unneccessarily duplicative." - **How to do this?**
- Resources available:
- 2013 research grant list
- 2012 services and research information from Report to Congress on ASD Activities
- Budgetary requirements – discuss in April?

Next Steps

- Determine working group composition and chairs?
- Select external experts?
- Via e-mail – brainstorm some topics to include under the Questions – discuss them in WGs
- Set working group meeting (conference call) schedule – February and March
- Review progress in April full committee meeting
- Complete update by July 2016 IACC meeting

OARC will:

- Contact IACC members to determine WG membership and chairs and select external experts
- Set a meeting schedule
- Prepare materials

IACC
INTERAGENCY AUTISM COORDINATING COMMITTEE

OFFICE OF AUTISM RESEARCH COORDINATION
NATIONAL INSTITUTES OF HEALTH

Susan Daniels, Ph.D., Director

Chumba Kitur, **B.A.**, Operations Coordinator

Karen Mowrer, Ph.D., Science Policy Analyst

Miguelina Perez, B.A., Management Analyst

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

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

Nam-Andrew Kim, B.S., UI/UX Designer

Meeting of the IACC

Lunch

Meeting of the IACC

Afternoon Agenda

1:15 PM **Oral Public Comment Session**

1:45 **IACC Committee Member Discussion**
Public Comments

2:45 **Break**

Meeting of the IACC

Oral Comments Session

DEVASTATING EFFECTS OF CHRONIC PARENTAL DENIAL IN AUTISM

NIH/NIMH/IAAC Full Committee Meeting 01/12/2016

By Dr. Linda VARSOU-PAPADIMITRIOU

Scientist, Ass. Professor, PhD, MPH, DABCC

Mother of a 30-year-old son with autism

THE AUTISM INTENSIVE
EXPERT INTERVIEW SERIES

http://theautismintensive.com/event

Gain Lifetime Access to All HD Video Interviews, MP3 Files and 350 pages of Transcripts for Just $79.95

“Parents know their children better than anyone”

YES

BUT

NOT IN AUTISM

BECAUSE

IN 50% OF FAMILIES AL LEAST ONE PARENT

IS IN “DENIAL” OF ITS CHILD AUTISM OR OF THE EXTEND OF ITS SEVERITY

Is anyone in the audience in denial?

Definitely NOT, because just the fact that you are here proves the opposite.

BUT

Because you are **NOT** in denial, you might ignore the family **prevalence of Chronic Parental Denial** of child's autism and the devastating effects to the child with autism who becomes the ultimate victim.

The entire family suffers as result of Chronic Denial from at least one parent, usually the father.

"Resolution of the Diagnosis Among Parents of Children with Autism Spectrum Disorder: Associations with Child and Parent Characteristics", J Autism Dev Disord (2010) 40:89–99

- This is the only paper from Israel, giving a prevalence of parents denial close to 53%.
- Taking out the bias of parents "volunteering" to this study, the actual prevalence must be much higher…..
- Prevalence of denial: 50% in Europe, 45% in USA (data provided by professionals in the field of autism, not from research)

Urgent need for studies on denial in autism and measures to be taken

- A study on “Denial in Autism”, will start soon in Greece, where parents consider Denial very serious issue, second only autism diagnosis.
- The study on Denial will be part of the **ASDEU project**, a new trans-European program initiated by Autism-Europe, to assess all issues related to Autism Spectrum Disorders in European Union
- Why not to collaborate and share research protocols on “Denial” with the NIH/NIMH/IACC?

Assess and include the factor of **Chronic Parental Autism DENIAL** to the Research Domain Criteria (RDoC) and to the 2016 Strategic Plan Objectives

IN ORDER

- To have more reliable studies and results in autism.
- To better understand and deal with autism issues.
- To avoid more autism related family dramas.
- To protect and save our children with autism from the deleterious effects Denial has.

Make “D e n i a l” in autism to be only ….a river in Egypt

Meeting of the IACC

IACC Committee Member Discussion of Public Comments

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

Meeting of the IACC

Break

Meeting of the IACC

Afternoon Agenda

3:00 PM **Autism Screening Panel**

David Grossman, M.D., M.P.H.
Senior Investigator, Group Health Research Institute
Medical Director, Population Health Strategy

Daniel L. Coury, M.D.
Chief, Section of Developmental and Behavioral Pediatrics
Nationwide Children's Hospital

Screening for Autism Spectrum Disorder in Young Children

David Grossman, M.D., MPH

Vice-Chair, US Preventive Services Task Force

U.S. Preventive Services TASK FORCE

Task Force Overview

- The U.S. Preventive Services Task Force’s recommendations are based on a rigorous review of existing peer-reviewed evidence and are intended to help primary care clinicians and patients decide together whether a preventive service is right for a patient's needs.

Task Force Overview (continued)

The U.S. Preventive Services Task Force …

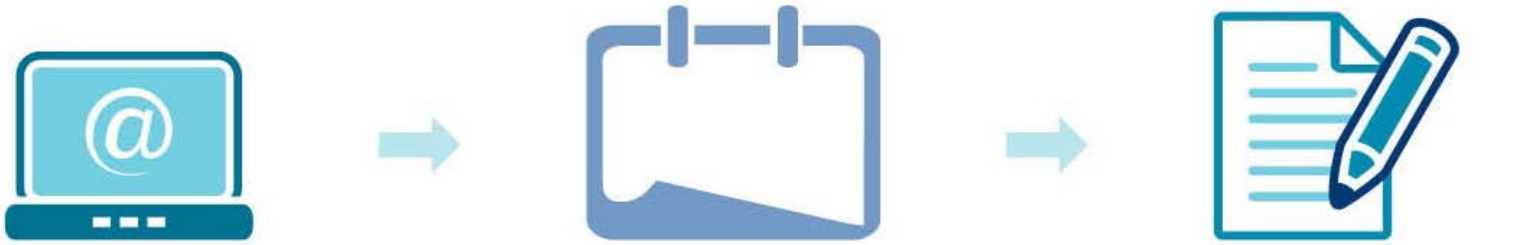
- Makes recommendations based on rigorous review of existing peer-reviewed evidence
  - Does not conduct the research studies, but reviews and assesses the research
  - Evaluates benefits and harms of each service based on factors such as age and sex
- Is an independent panel of experts in prevention and evidence-based medicine
- Methodology is transparent and available on website. Same methods used for all preventive services for children and adults.

Task Force Recommendation Grades

Grade	Definition
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

Draft Recommendation Process

- To develop a recommendation statement, Task Force members consider the best available science and research on a topic. For each topic, the Task Force posts draft documents for public comment, including the **draft recommendation statement**. All comments are reviewed and considered in developing the final recommendation statement.



The Task Force welcomes comments on this draft recommendation.

Comments must be submitted during the four-week public comment period.

All comments will be considered for use in writing final recommendations.

Screening for Autism Spectrum Disorder

- In August, the Task Force issued, for the first time, a draft recommendation statement on screening for autism in young children.
- The Task Force cares deeply about helping children with autism and their families get the care and support they need.

Autism Spectrum Disorder in Children Under Age Three Years: Screening

Draft Recommendation August 2015

- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for autism spectrum disorder (ASD) in children for whom no concerns of ASD have been raised by their parents or clinical provider.

This is an

I

statement.

This draft recommendation was posted for public comment at www.uspreventiveservicestaskforce.org/tfcomment from Aug. 3-Aug. 31, 2015.

Autism Spectrum Disorder in Children Under Age Three Years: Screening

Draft Recommendation □ August 2015 □ Clarifications

- An I Statement is NOT a recommendation against screening
  - An I Statement is <u>a call for additional research to close specific gaps identified</u>
    - High-quality evidence with internal and external validity for the benefits of treatment is inadequate for children under age 3 and screen-detected populations
  - Gaps identified from 'I' statements are high-priority areas and are outlined in an annual Report to Congress
  - USPSTF finds that potential harms of screening and behavioral treatments are likely low

Autism Spectrum Disorder in Children Age Three Years: Screening

Draft Recommendation □ August 2015 □ Clarifications

- Clinicians are advised to use clinical judgment in areas of uncertainty around screening
- I Statement on autism screening from the USPSTF will not influence insurance coverage
    - The ACA mandates coverage for autism screening based on the Bright Futures recommendation
- Task Force recommendations, including I Statements, do not apply to case-finding, or the type of targeted testing used to follow up on concerns raised by parents, caregivers or a child's healthcare provider

Autism Spectrum Disorder in Children Under Age Three Years: Screening

- Trial designs are available that would help close the research gaps:
  - Randomized screening trials with invitation to screen in early childhood
    - Vs. no screening
    - Vs. late screening
    - Vs. late vs. no screening
  - OR: Randomized trials focused on treatment of 1-3 year old children identified through screening

Summary

- USPSTF believes that important research progress has been made in the areas of :
  - Treatment trials of clinically identified, older children
  - Identification of accurate and valid screening tools
- The ideal scientific trajectory is:

Clinical identification → Treatment trials → Screening tests development → Screening trials → Screening programs

Summary

- The Task Force believes that children and their families deserve to know what works when it comes to screening for autism
  - We owe it to our children to execute high-quality studies that can help us fill in the research gaps
- The Task Force applauds the work the IACC partners have done thus far to help identify potential causes of, tools for diagnosis of, and potential treatments for autism
  - The next step is to focus research efforts on new trials

Thank you for your interest

www.USPreventiveServicesTaskForce.org

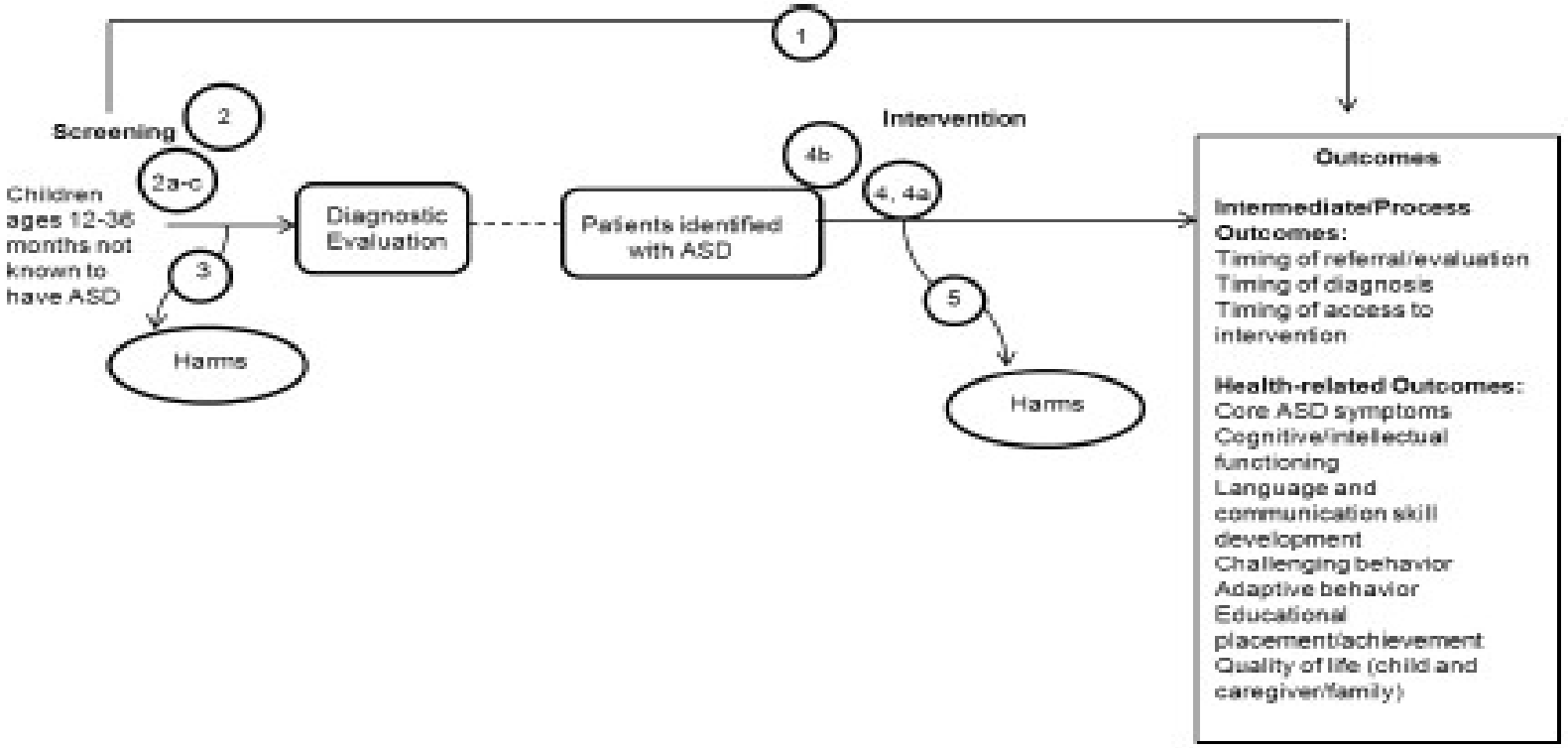
Autism Spectrum Disorder in Children Under Age Three Years: Screening

Draft Recommendation □ August 2015 □ Supporting Evidence

- What USPSTF does NOT do:
  - Use expert opinion to make recommendations when faced with inadequate evidence
  - Extrapolate evidence
  - Make insurance coverage recommendations

Autism Spectrum Disorder in Children Under Age Three Years: Screening

Draft Recommendation August 2015



Note: Numbers in circles on the diagram refer to key questions.

Abbreviation: ASD=autism spectrum disorder.

Autism Spectrum Disorder in Children Under Age Three Years: Screening

Criteria Used for Judging Adequacy of an Evidence Base:

1.Do the studies have the appropriate research design to answer the key question(s)?

2.To what extent are the existing studies of sufficient quality (i.e., what is the internal validity)?

3.To what extent are the results of the studies generalizable to the general U.S. primary care population of interest to the intervention and situation (i.e., what is the applicability)?

4.How many and how large are the studies that address the key question(s)? Are the results precise?

5. How consistent are the results of the studies?

6. Biologic Plausibilty

WHO Criteria for Screening Program Feasibility

- Does this disease represent a significant health problem (morbidity, mortality, prevalence, quality of life, etc)?
- Is there an effective treatment for it?
- Does earlier intervention lead to a better outcome?
  - Is the natural history of the disease known, and is there a recognizable latent stage or early symptomatic stage during which screening could be applied?
  - Will treatment at this early stage decrease mortality and morbidity? For what fraction of cases?
- Is there a screening test that is valid, suitable and acceptable?
- Is there a defined population that can benefit from the screening program? Who are they?
- Is the optimal interval between screening tests known?

ASD Screening in Clinical Practice: Considerations for the USPSTF

Daniel L. Coury MD, FAAP
Professor of Pediatrics and Psychiatry
The Ohio State University

Brief Summary Statement

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for autism spectrum disorder (ASD) in children for whom no concerns of ASD have been raised by their parents or clinical provider.

(elsewhere described as "asymptomatic")

Pitfalls with “no concerns”

Parental concern or lack of concern is not infallible

- many parents do not recognize signs of developmental delay in walking, talking, etc.[1]
- reasons behind this are several including lack of knowledge and cultural factors [2,3]

[1]King et al, J Dev Behav Pediatr 2005; 26:293-303

[2]Mazurek et al, J Dev Behav Pediatr 2014;35:561-569.

[3]Zuckerman et al, J Dev Behav Pediatr 2014;35:522-532

Pitfalls with “no concerns”

Physician concern or lack of concern is not infallible

- Clinical impression / developmental surveillance is not as accurate as formal screening [1]
- Children with ASD may not display ASD behaviors during course of visit [2]
  - May display typical behavior up to 89% of time
  - Expert raters may miss diagnosis up to 40% of time

[1] Werner et al, Child Dev 1968;39:1063-1075.

[2] Gabrielsen et al, Pediatrics 2015; 135:e330-e338.

Pitfalls with “no concerns”

“In general, children identified through screening rather than through case finding are likely to be younger and possibly less severely affected… It is therefore unclear whether young children with ASD detected by screening and not because of parental or teacher concern will experience similar, or any, benefit.”

Pitfalls with “no concerns”

- Most evidence suggests that more mildly affected children respond even more positively to treatment [1]
- There is no evidence that children with autism who are identified through systematic screening, rather than expression of parent concern, are less severely impaired.

[1] Warren et al, A systematic review of early intensive intervention for autism spectrum disorders. Pediatrics 2011;127(5): e1303–e1311

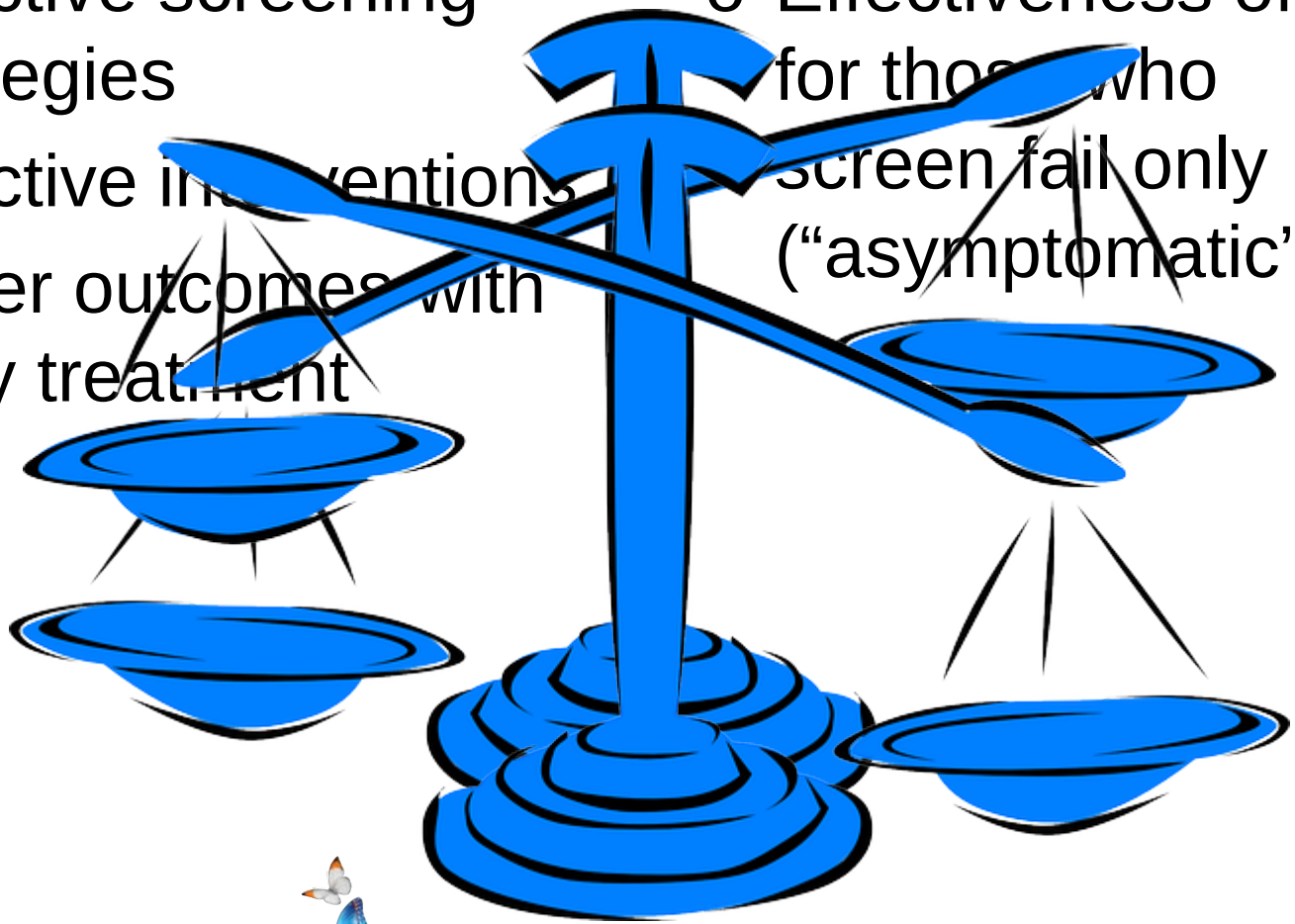
The USPSTF concludes there is insufficient evidence to assess the benefits of screening for ASD. The balance of benefits and harms cannot be determined.

Evidence is Present

- ✓ Effective screening strategies
- ✓ Effective interventions
- ✓ Better outcomes with early treatment

Evidence is Lacking

- o Effectiveness of EI for those who screen fail only ("asymptomatic")



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

Unintended Consequences

- The wording regarding insufficient evidence is too easily interpreted as “there is no need to do this”
- We do have evidence that we are already missing children with developmental and ASD concerns with our current screening processes; we should not be making this worse

Unintended Consequences

- Under the Affordable Care Act, insurers must cover the full cost of preventive services that are recommended by the task force on the basis of strong evidence.
- If its recommendation is based on evidence that gets an A or B, then federal law requires insurers to go along.
- If, however, the evidence is weaker and gets a C or worse, then there's no mandate for free coverage. Screening in general may decrease, worsening the current situation.

Meeting of the IACC

Afternoon Agenda

Autism Screening Panel – Continued

Diana L. Robins, Ph.D.
Research Program Area Leader, Early Detection and Intervention for Autism Spectrum Disorder (ASD)
Associate Professor, A.J. Drexel Autism Institute

Karen Pierce, Ph.D.
Associate Professor, Department of Neurosciences
University of California, San Diego (UCSD)

Meeting of the IACC

Afternoon Agenda

Autism Screening Panel – Continued

Amy M. Wetherby, Ph.D.
Director, Autism Institute in the College of Medicine
Florida State University

Review of Screening Studies

Diana L. Robins, Ph.D.
Associate Professor
Early Detection & Intervention
Research Program Leader
AJ Drexel Autism Institute
Drexel University

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research

Lonnie Zwaigenbaum, Margaret L. Bauman, Deborah Fein, Karen Pierce, Timothy Buie, Patricia A. Davis, Craig Newschaffer, Diana L. Robins, Amy Wetherby, Roula Choueiri, Connie Kasari, Wendy L. Stone, Nurit Yirmiya, Annette Estes, Robin L. Hansen, James C. McPartland, Marvin R. Natowicz, Alice Carter, Doreen Granpeesheh, Zoe Mailloux, Susanne Smith Roley and Sheldon Wagner

Pediatrics 2015;136;S41
DOI: 10.1542/peds.2014-3667D

Summary of Screening Literature

Measure	# Papers*
FYI - First Year Inventory	3
ITC - CSBS Infant Toddler Checklist	4
CHAT - Checklist for Autism in Toddlers	3
M-CHAT - Modified Checklist for Autism in Toddlers	11
M-CHAT-R/F - Modified Checklist for Autism in Toddlers, Revised, with Follow-Up	1
Q-CHAT - Quantitative Checklist for Autism in Toddlers	1
ESAT - Early Screening of Autistic Traits - Netherlands	3
YACHT - Young Autism and other Developmental Disorders Checkup Tool - Japan	1

*Low risk (Level 1) samples, including children younger than 2 years old

Sources: USPSTF Evidence Report, Zwaigenbaum et al., 2015

A Closer Look at 4 Studies Rated as **Good** Quality - USPSTF Evidence Report

	Tool	n	Age (mos)	Sens	Spec	PPV-ASD	PPV-any*	LR+
1.	**ITC**	10,479	10-15.9			.174	.723	
2.	**ITC**	5,385	6-24					
3.	**M-CHAT/F**	18,989	16-30.9	.91		.54	.975	
4.	**M-CHAT-R/F**	16,115	16-30.9	.854	.993	.48	.95	114.05

1. Pierce et al., 2011
2. Wetherby et al., 2008
3. Chlebowski et al., 2013; Kleinman et al., 2008
4. Robins et al., 2014

*PPV any developmental disorders or concerns

Universal Screening Reduces Disparity

Journal of Developmental & Behavioral Pediatrics
Official Journal of the Society for Developmental and Behavioral Pediatrics

Original Article

Standardized Screening Facilitates Timely Diagnosis of Autism Spectrum Disorders in a Diverse Sample of Low-Risk Toddlers

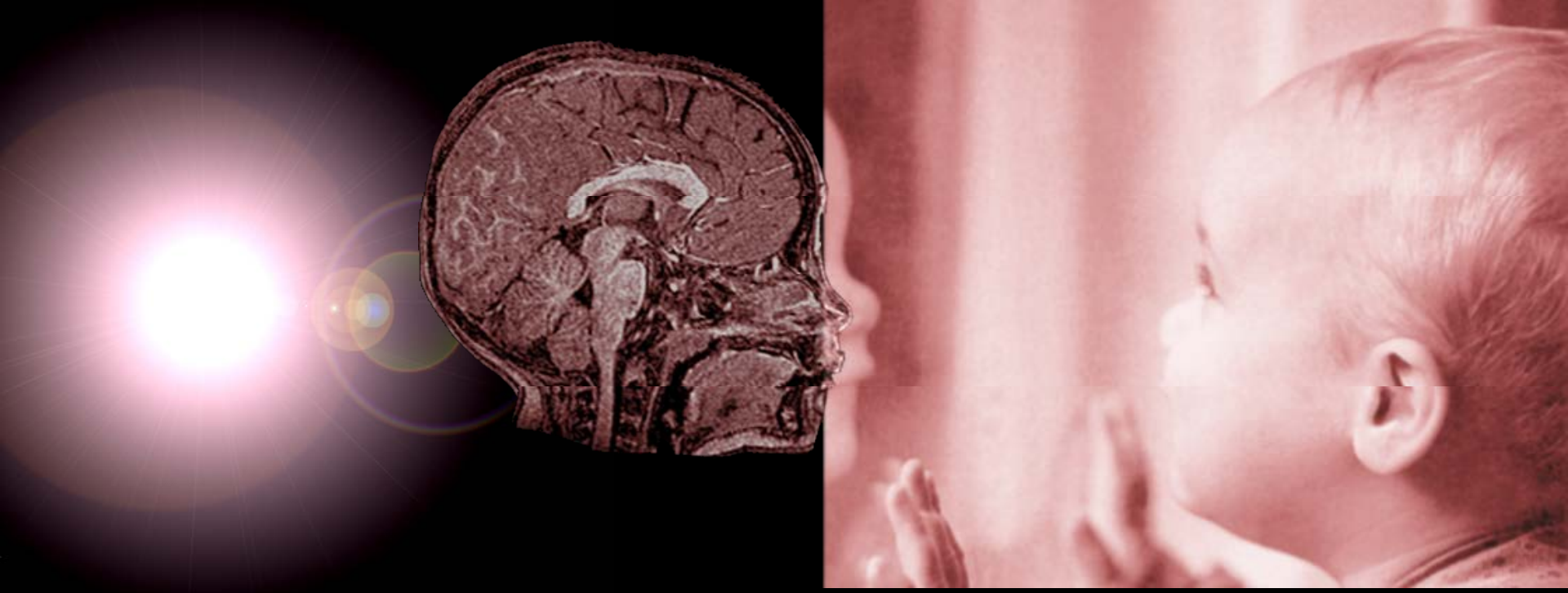
Lauren E. Herlihy, MA,* Bianca Brooks, BA,† Thyde Dumont-Mathieu, MD,*
Marianne L. Barton, PhD,* Deborah Fein, PhD,* Chi-Ming Chen, PhD,* Diana L. Robins, PhD†

2014; 35: 85-92

Age at Diagnosis		
Minority	Non-Minority	
26.28 (4.42)	25.20 (4.48)	t(341)=-2.26, p<.05

Summary of Findings from Screening Literature

- Evidence supports the usefulness of ASD-specific screening at 18 and 24 months (Zwaigenbaum et al., 2015)
- Adequate evidence demonstrates that currently available screening tools detect ASD in toddlers (USPSTF, 2015)
- Many children identified by screening **BEFORE** parents or physicians express concern (USPSTF Evidence Report, 2015, p. 47)



The Importance of Standardized Early Screening from a Biological and Basic Science Perspective

Karen Pierce, Ph.D.

Department of Neurosciences, UCSD

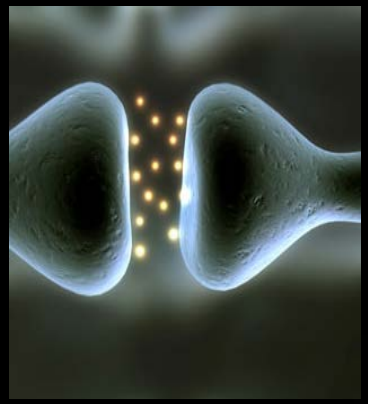
Autism Center of Excellence at:
www.autism-center.ucsd.edu

UC San Diego
SCHOOL OF MEDICINE

Early Enrichment, Animal Models, and Brain Plasticity

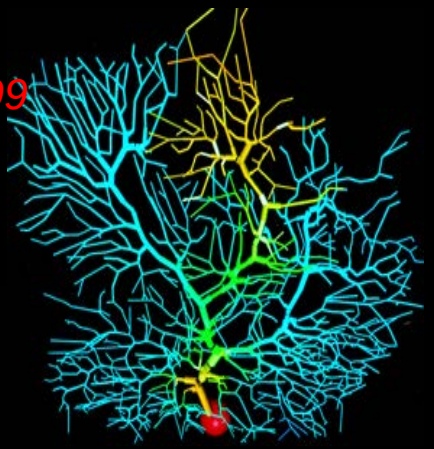
SYNAPSES

Rampon et al., 2000
Turner et al., 2003
Greenough
and Chang, Review



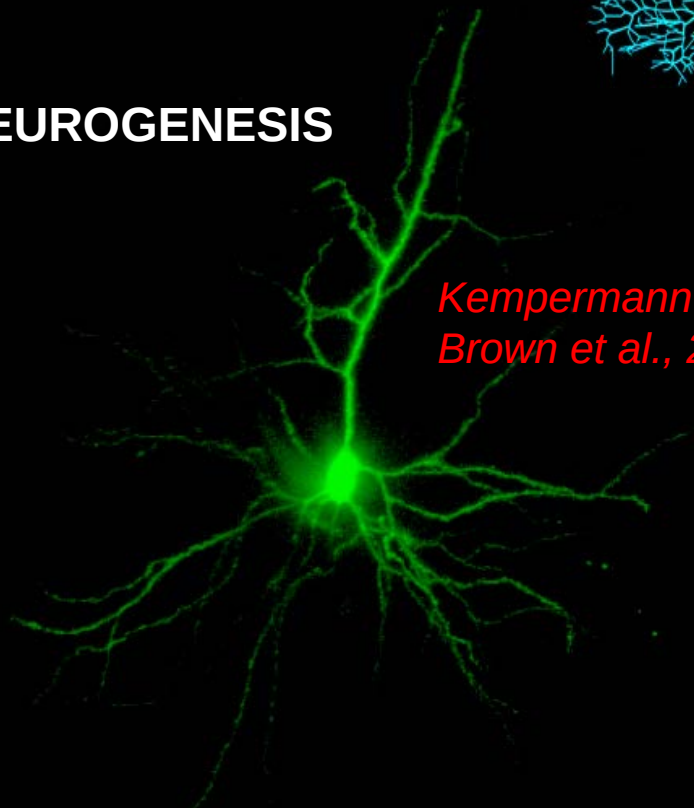
DENDRITIC BRANCHING

Nilsson et al., 1999
Greenough et al., 1986

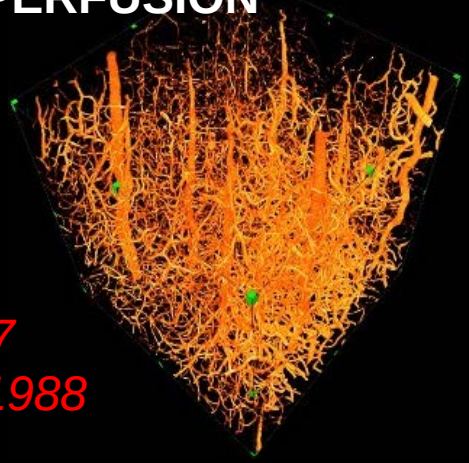


NEUROGENESIS

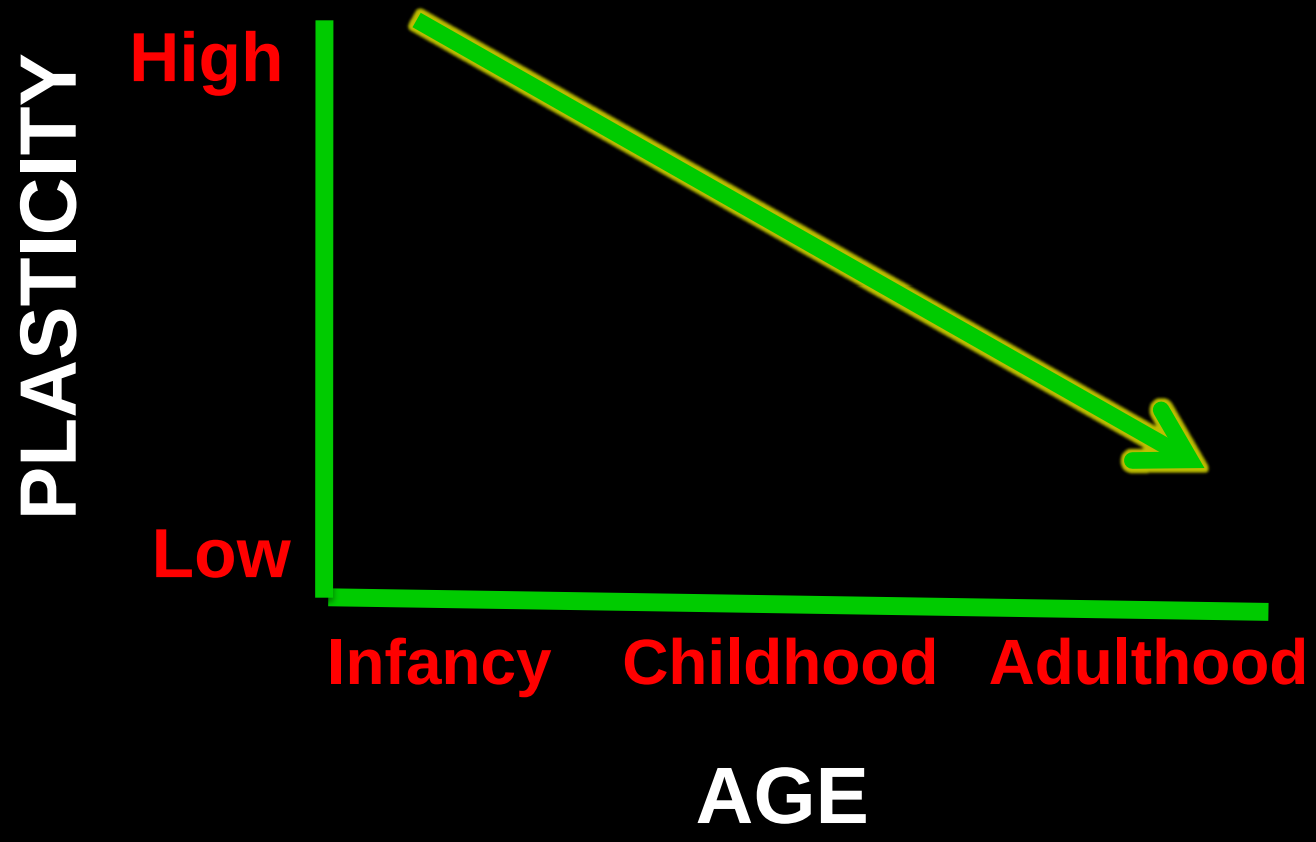
Kempermann et al, 1997
Brown et al., 2003

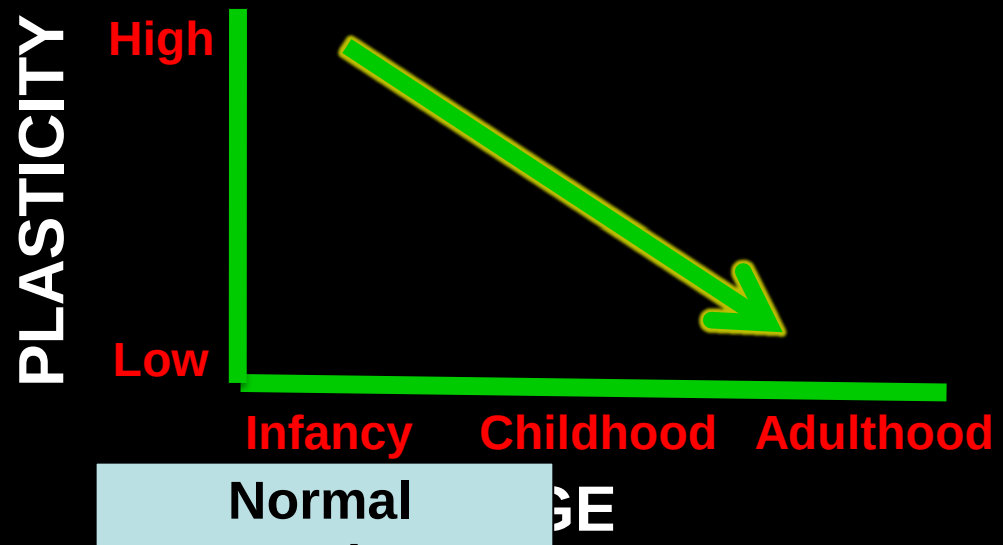


CAPILLARY PERFUSION

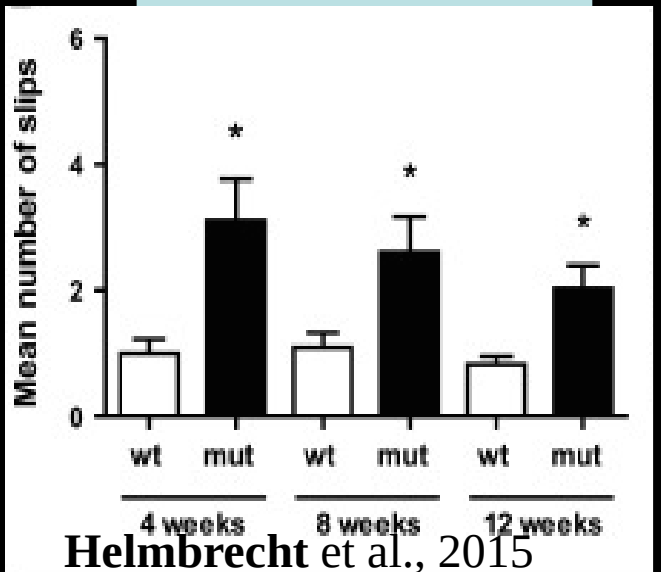


Black et al., 1987
Sirevaag et al., 1988


PLASTICITY
High
Low
Infancy
Childhood
Adulthood
AGE



Normal Housing (No Enrichment) :Rat with mutation slips more



Helmbrecht et al., 2015

CRITICAL PERIODS:
Lessons from Bucharest Early Intervention Project

Nelson et al., *Science*, (2007)

SUBJECTS

- 136 infants abandoned at birth in Bucharest, Romania and institutionalized

- 68 Foster Care (FCG)

- 68 Remained Institutionalized (IG)

- 72 Never Institutionalized (NIG) reared at Home with Biological Parents

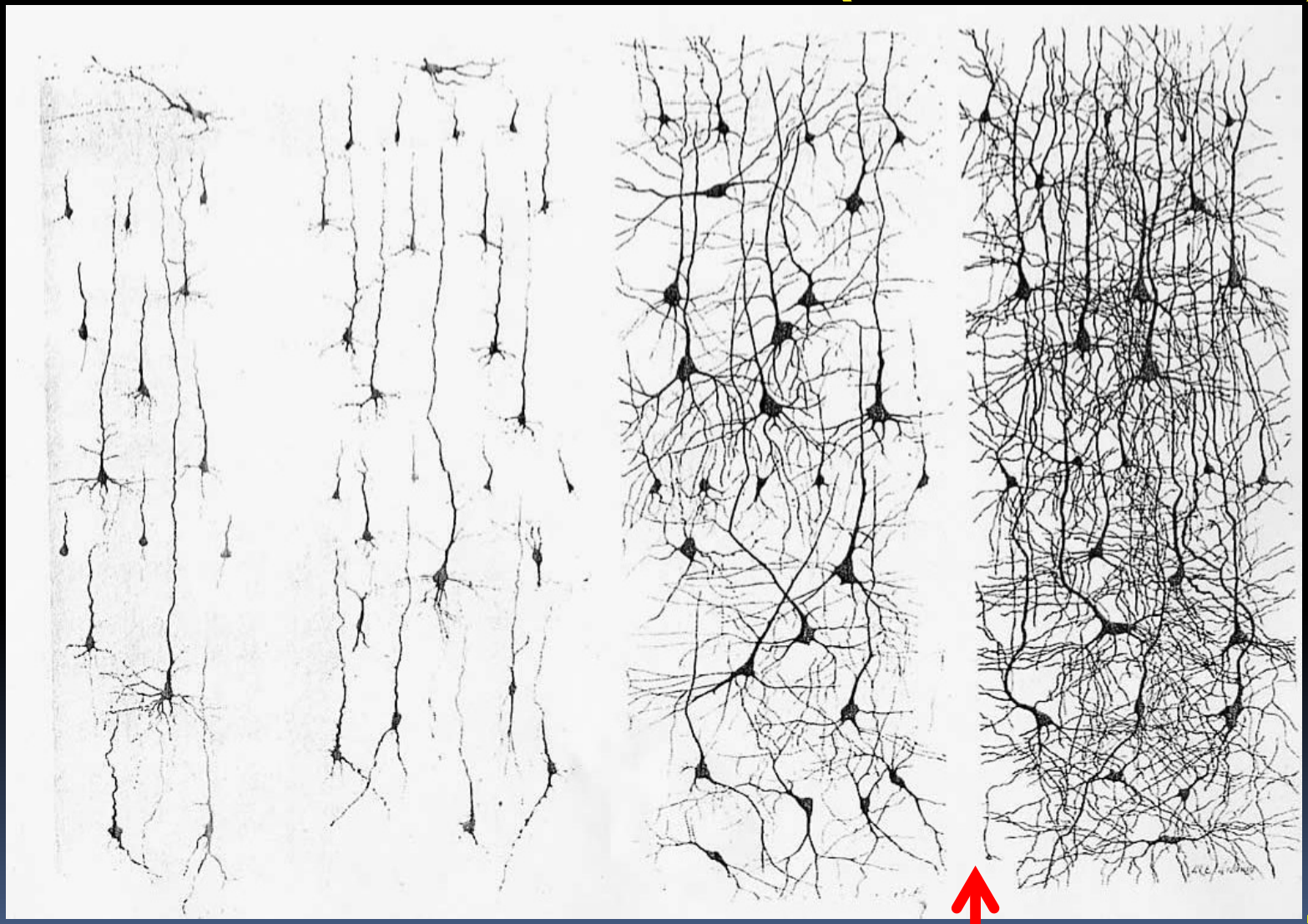
Results: Bucharest Early Intervention Project

GROUP MEAN D.Q.	
Institution (IG)- 42 mo	77.1
Foster Care Group- 42 mo	85.6
Never Institutionalized (NIG) 42 mo	103.4

Foster Care DQ at 42 months BY AGE OF PLACEMENT

AGE AT PLACEMENT	N	MEAN D.Q.
0-18	14	94.9
18-24	16	89.0
24-30	22	80.1
30+	9	79.7

Human Frontal Cortex Neural Development & Circuit Formation (Conel J.L. 1939)



Autism Diagnosis

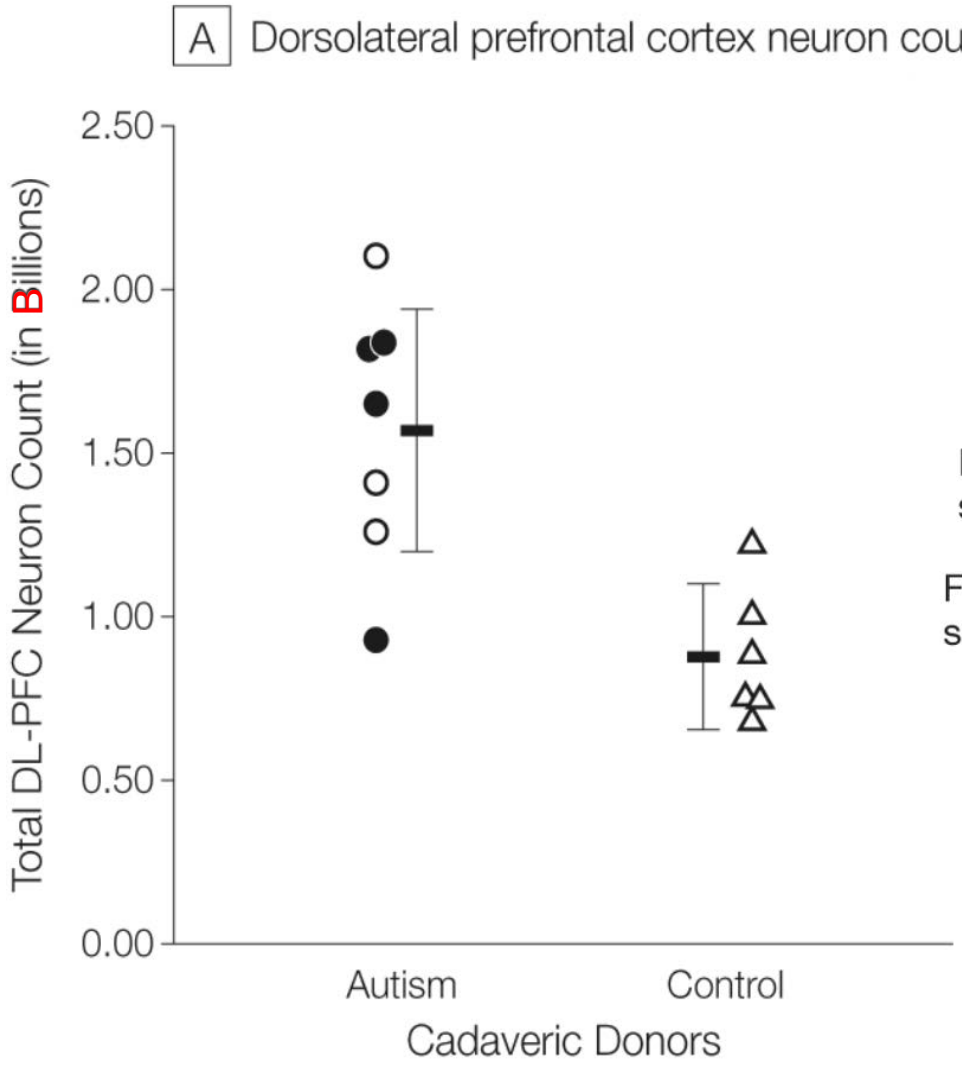
newborn 1 month 6 months 2 years 3-4 years

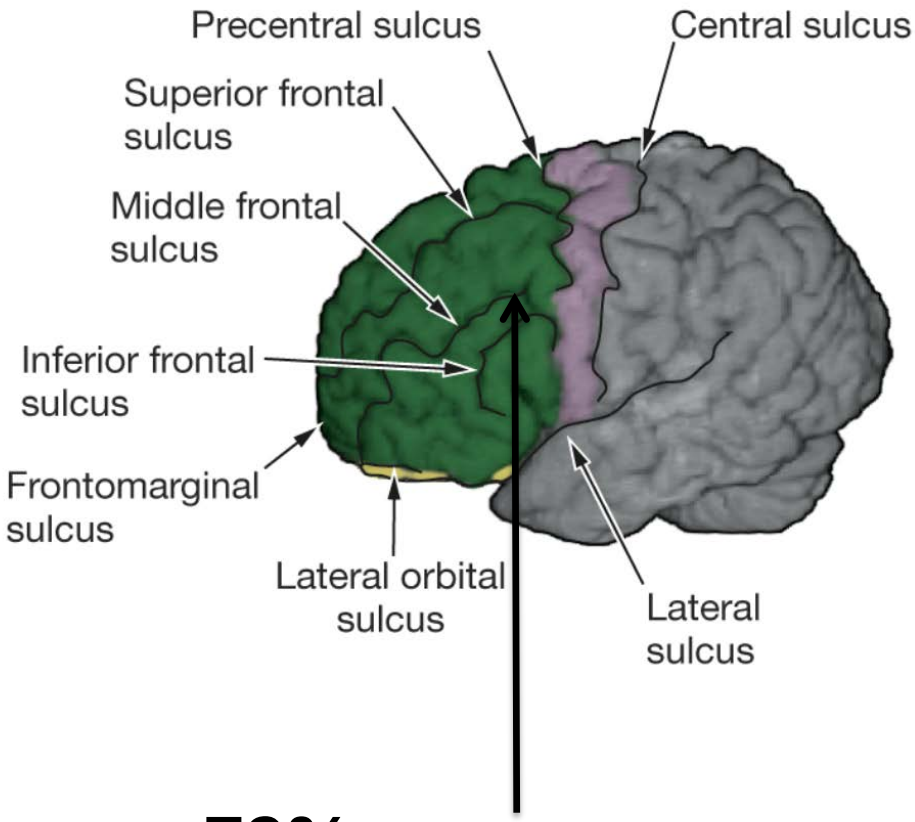
Point #1:

The Human Brain Undergoes Massive and Rapid Changes During the First Few Years of Life:

Can we take the chance to miss this window?

When Does Autism Begin?



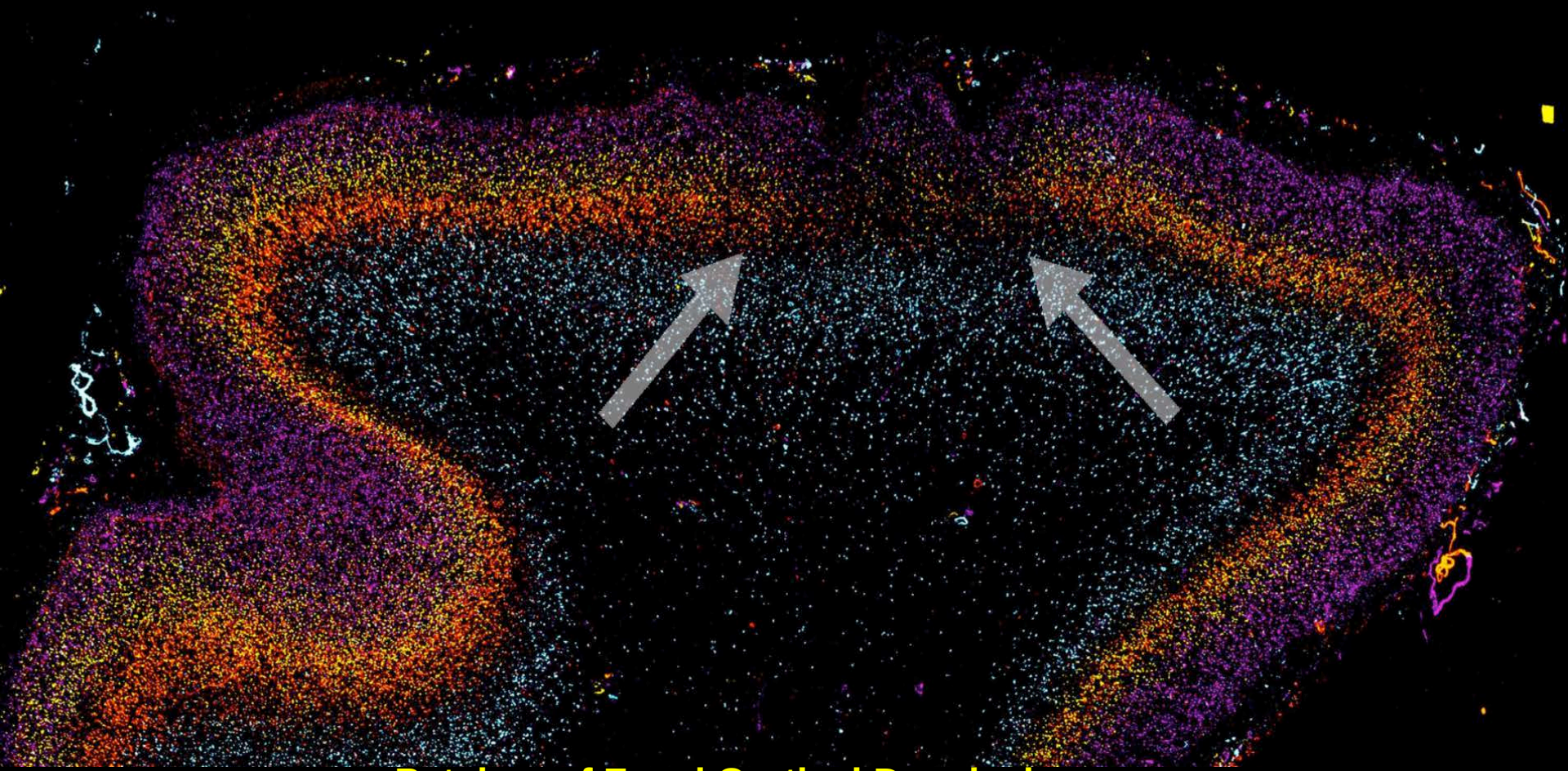


79% more neurons

Courchesne et al., 2011 JAMA

When Does Autism Begin?

We identified regions of tissue with abnormal labeling across multiple layers in autistic cortex



Patches of Focal Cortical Dysplasia:
Abnormal Laminar Organization, Migration Defects and Clusters of Disoriented Cells

Stoner et al., NEJM, 2013

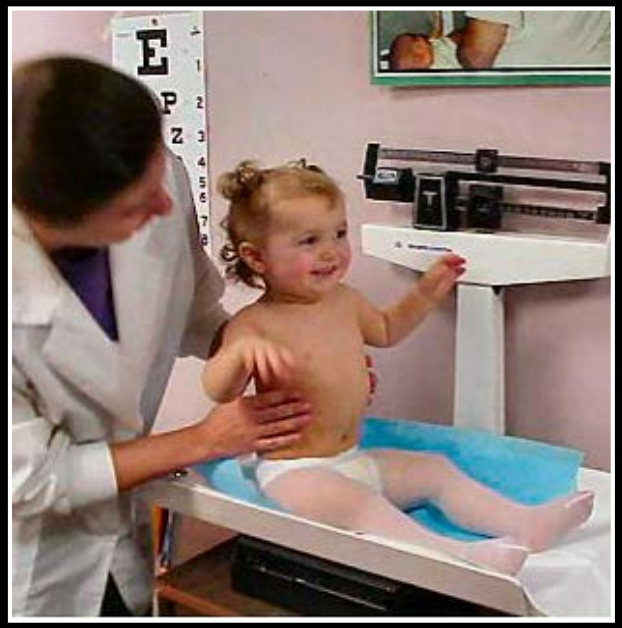
Point #2:
Biologically, autism most likely begins in the womb

Should we wait years to start treatment?

Studying Autism Prospectively:
The 1Yr Well-Baby Check-Up Approach – GET SET Early Model

Pierce, et al., (2011) J. Pediatrics

1-Yr. Check-Up Approach



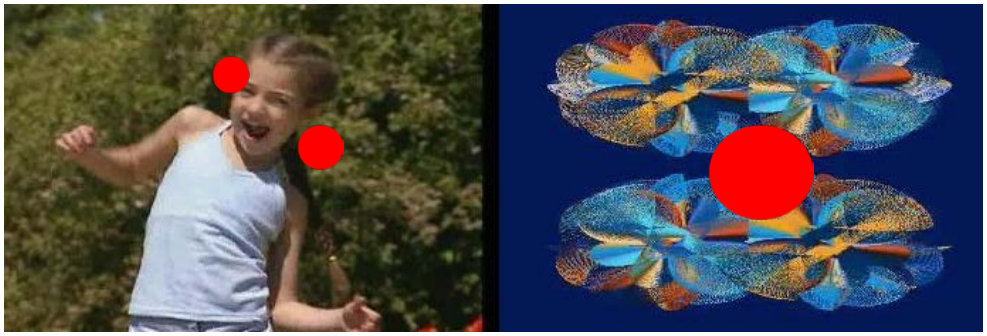
Rationale:
Administer a broad-band CSBS screen to detect *all* cases of delay at 12-months at routine pediatric check up → a % of cases will end up with ASD.

- **Network of 170 Peds**
- **60,000 Screened to date**
- **Average age Tx Start: 17 months**

Early Biomarkers of ASD Can Not Be Discovered Without Early Detected Cohorts from General Population

- **Eye Tracking Based**

Eye Gaze Fixation Patterns

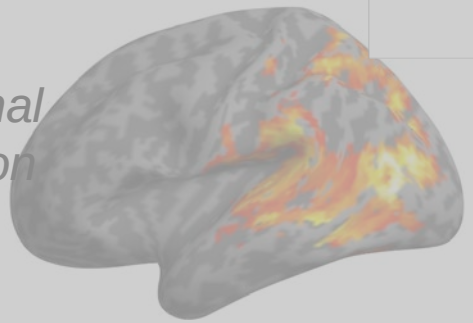


Geo Pref Test

- **Neuroimaging Based**

EEG: Bosl et al., 2011, *BMC Medicine*
fMRI: Lombardo et al., 2015, *Neuron*

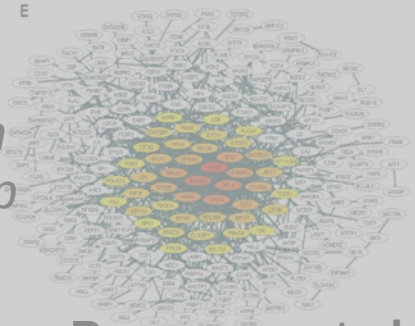
Functional Activation Map



- **Blood Based**

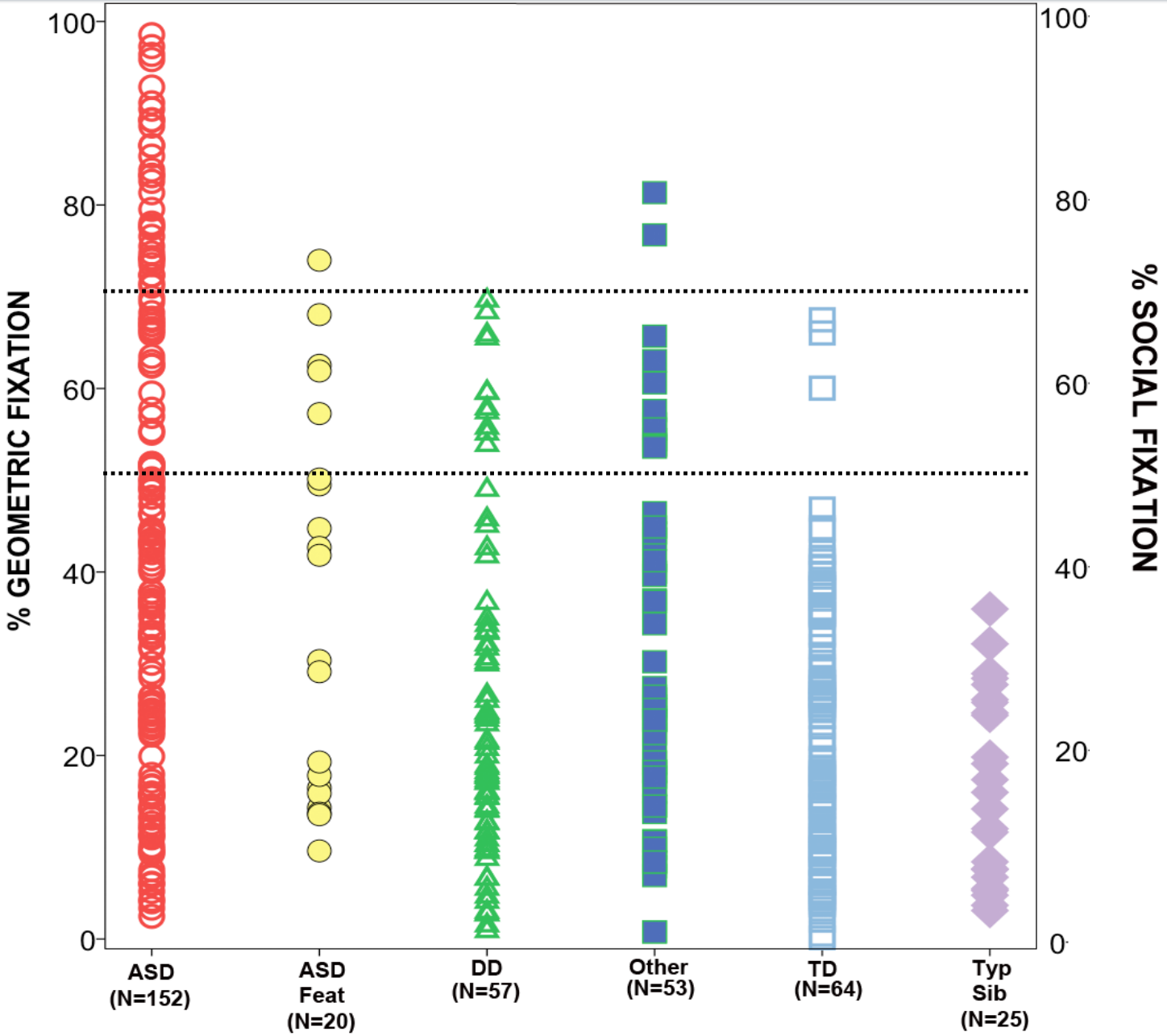
DNA
RNA
Proteomics

Protein-Protein Interaction map



Pramparo et al.., 2015

N=444 From a Screened Cohort

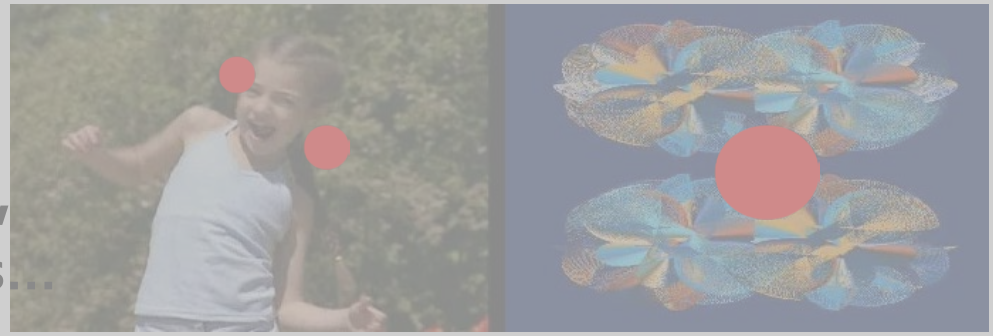


Early Biomarkers of ASD Can Not Be Discovered Without Early Detected Cohorts from General Population

- **Eye Tracking Based**

N=444, specificity for ASD 98%, 12 months, 13 months, 14 months…

Pierce et al.., 2015 , *Biological Psychiatry*

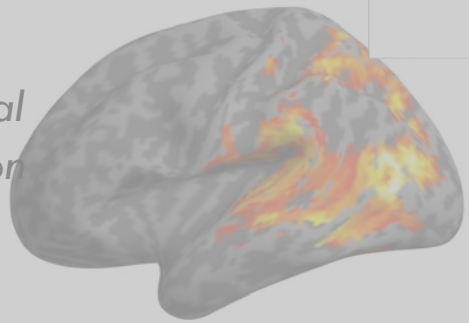


Geo Pref Test

- **Neuroimaging Based**

fMRI: Lombardo et al., 2015, *Neuron*

Functional Activation Map



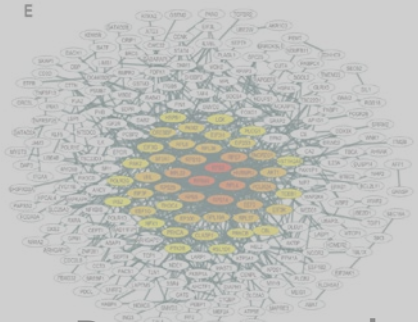
- **Blood Based**

DNA

RNA

Proteomics

Protein-Protein Interaction map



Pramparo et al.., 2015

Screened Cohorts Reveal Biomarkers of Prognosis

N=103

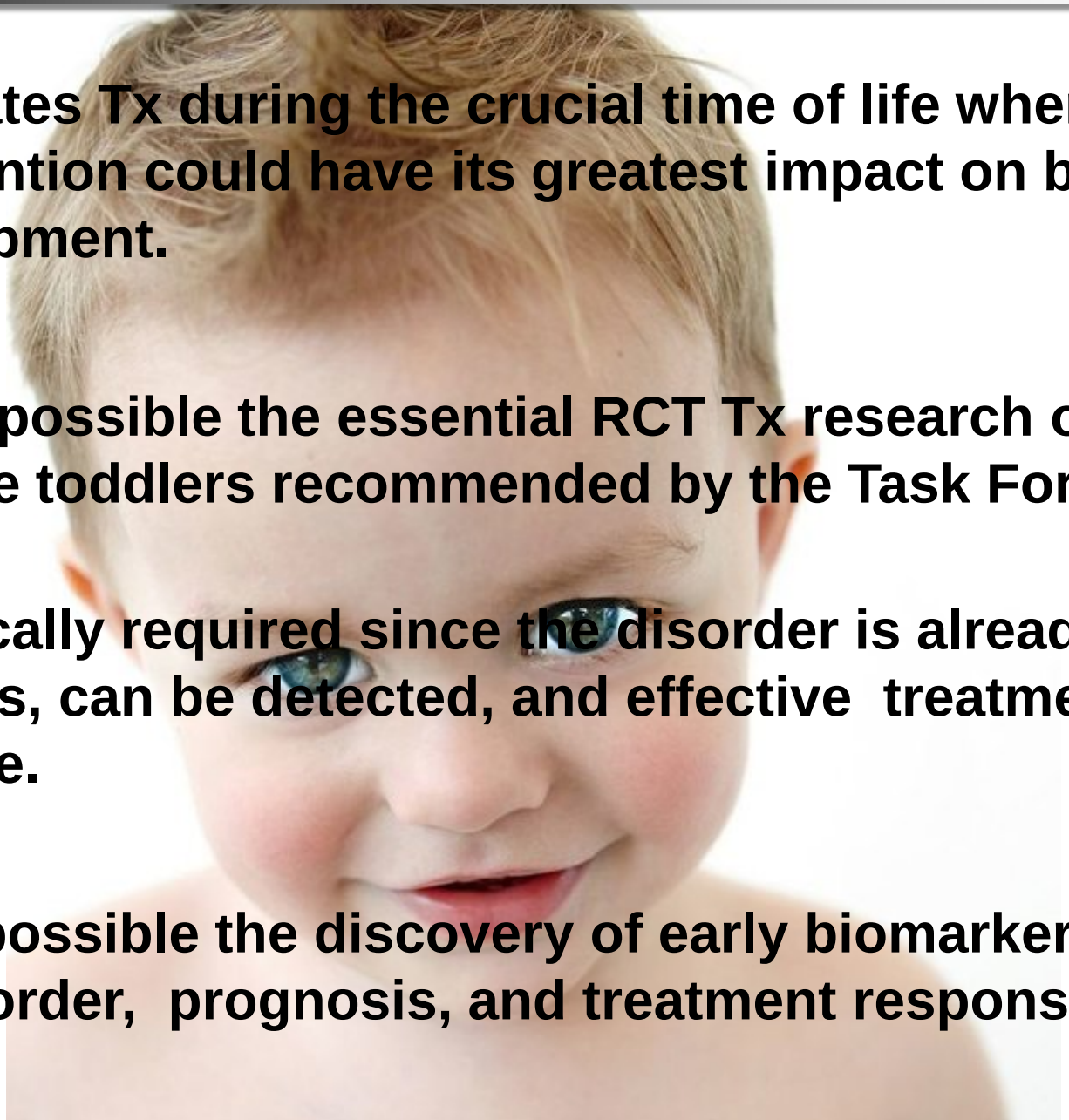
TYPICAL

Lombardo et al., (2015) Neuron

Point #3:

Standard of Care Screening Facilitates Important Discoveries Regarding Early ASD

THE BENEFITS OF EARLY SCREENING



1. **Facilitates Tx during the crucial time of life when intervention could have its greatest impact on brain development.**

2. **Makes possible the essential RCT Tx research of screen positive toddlers recommended by the Task Force.**

3. **Is ethically required since the disorder is already in progress, can be detected, and effective treatments available.**

4. **Makes possible the discovery of early biomarkers of the disorder, prognosis, and treatment responsiveness**

Overcoming Challenges of Early Screening for Autism in Primary Care

Amy M. Wetherby, PhD
Distinguished Research Professor
Laurel Schendel Professor of Communication Disorders
Director, Autism Institute
College of Medicine, Florida State University

Meeting of the Interagency Autism Coordinating Committee

January 12, 2016

Bethesda, Maryland

Research in a Nutshell
Treatment Studies of Toddlers with ASD

Early Intervention for Children With Autism Spectrum Disorder Under 3 Years of Age: Recommendations for Practice and Research

Zwaigenbaum et al. *Pediatrics* 2015; 136:S60-S81

- Review of 24 interventions for children with ASD < 3 years published from 2000-2013 identified comprehensive and targeted treatment models with evidence of clear benefits.
- Emphasized the central role of the parent and interventions designed to incorporate learning opportunities into everyday activities, capitalize on “teachable moments” and facilitate the generalization of skills.

Treatment Studies of Toddlers with ASD Do Not Separate Cases Recruited from Primary Care

Ascertainment Methods to Recruit Families
➢ Referral for Suspected ASD
➢ Screening for ASD in Early Intervention
➢ Younger Siblings of Children with ASD
➢ Screening for ASD in Primary Care Settings

Research in a Nutshell
Treatment Studies of Toddlers with ASD

Parent-Implemented Social Intervention for Toddlers With Autism: An RCT
Amy M. Wetherby, Whitney Guthrie, Juliann Woods, Christopher Schatschneider, Renee D. Holland, Lindee Morgan and Catherine Lord
Pediatrics; originally published online November 3, 2014;

Pediatrics 2015; 136:S60-S81

Wetherby et al. (2014) – RCT of 82 toddlers diagnosed with ASD at 18 months demonstrated significant differential treatment effects of a parent-implemented intervention

- 43 toddlers were referred for suspected ASD at UM site; 39 were recruited from screening in primary care at FSU site
- Site differences in cognitive level (=72 vs. 77 ELC on Mullen) but no site differences in treatment effects

How many children were missed?

Screener	Sample Size	Age in months	Hits	# per 1,000
CHAT Baird et al., 2000	16,235	m=18.7	33	2.03
M-CHAT Chlebowski et al., 2013	18,122	m=20.4	95	5.24
M-CHAT Stenberg et al., 2014	52,026	at 18	60	1.15
ESAT Dietz et al., 2006	31,724	m=14.9	18	0.57
ITC Wetherby et al., 2008	5,385	m=16.4	60	11.14

Selection Bias of Screening Samples for Estimates of Sensitivity and Specificity

- Intellectual ability or developmental level is an indication of how representative the sample is
- Percentage of children with average or above average IQ has increased to at least half
- Selection bias if the average developmental level is far below 75
  - Ozonoff et al. (2015): Mullen ELC=79 (*n*=38)
  - Robins et al. (2014): Mullen ELC = 68 (*n*=105)
  - Wetherby et al. (2008): Mullen ELC = 73 (*n*=60)

Need to Improve Early Identification of Developmental Disabilities

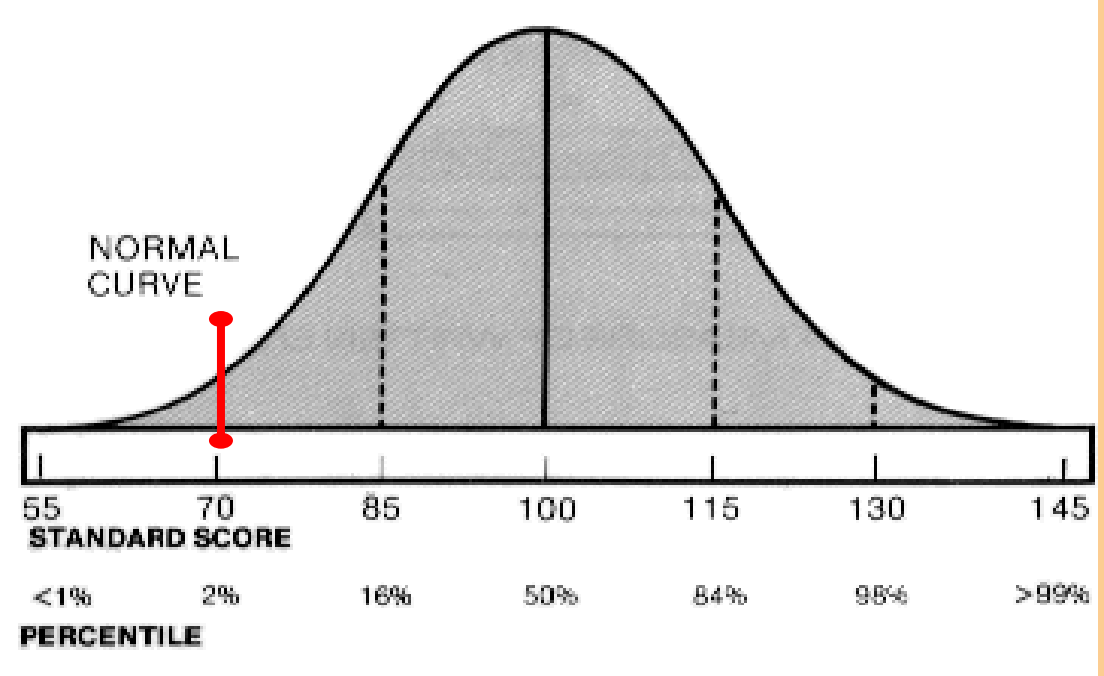
Percentage of Population Receiving Special Education or Early Intervention Services in 2007:

- School-Age Children
  6 to 17 years 11.4%
- Preschool Children
  3 to 5 years 5.7%
- Infants and Toddlers
  Birth to 2 years 2.5%

✓ This means, 80% of children are missed.

(31st Annual Report to Congress, US DOE OSEP, 2012)

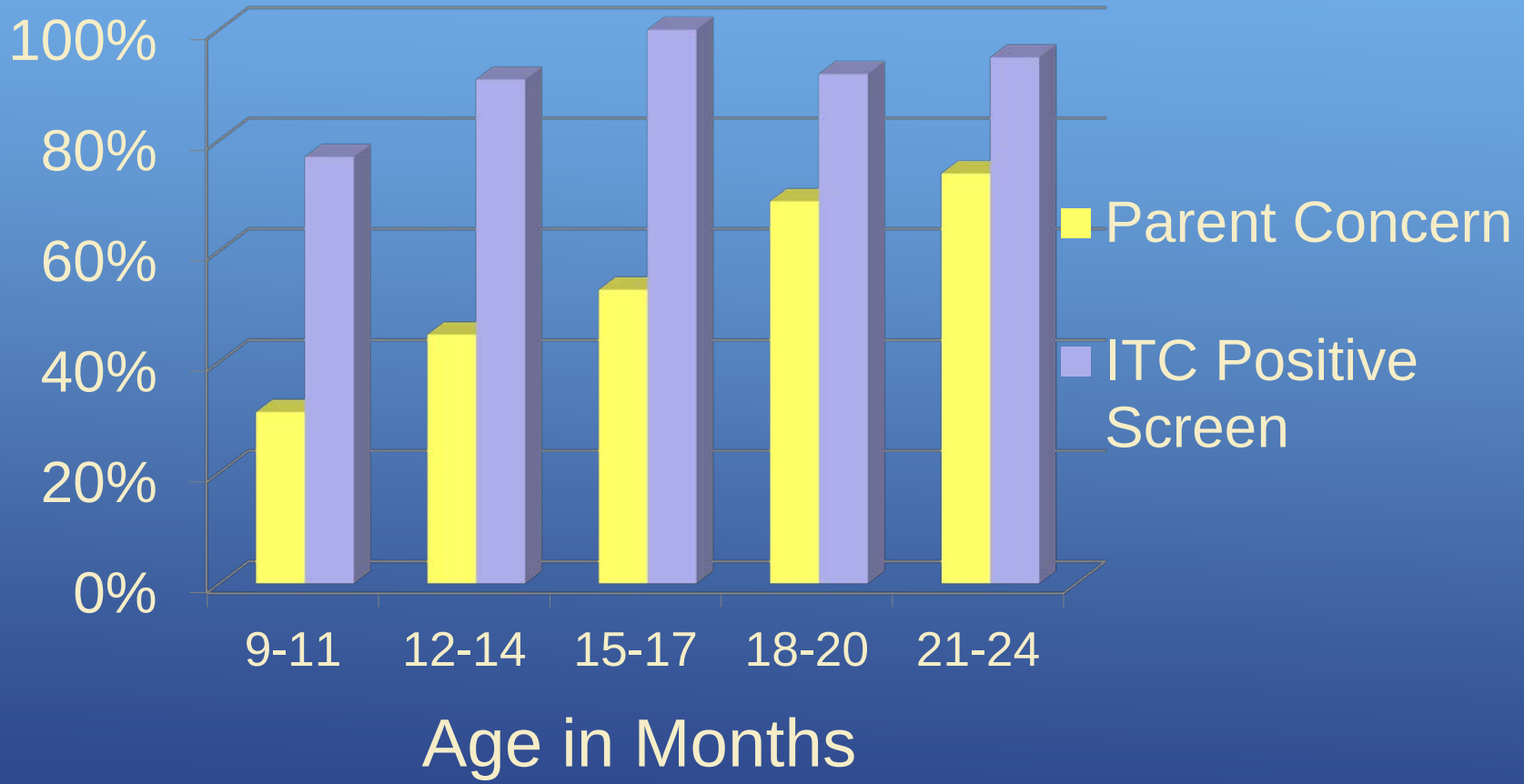
Where do we draw the line?



SD	SS	%ile
0.00	100	50th
-1.00	85	16th
-1.25	81	10th
-1.50	77	7th
-2.00	70	2nd

2nd percentile is too low to detect the 11.4% who will be eligible for special education at school age in time for early intervention.

Parent Concern & Positive Screen on the Infant-Toddler Checklist for Children with ASD (*n*=60)



Wetherby, Brosnan-Maddox, Peace, & Newton, 2008

Parent Concern is Less Accurate for Children at Younger Ages

- Retrospective and prospective studies of parents of children with ASD show:
  - About 75% have concerns by 24 months
  - About 50% have concerns by 18 months
  - About 30% have concerns by 12 months
- Reported concerns not usually specific to autism
- Parents are fairly accurate reporting what their child can and cannot do but not as accurate at knowing when to be concerned.

Focus Groups with Families (n=105): Overcoming Barriers to Improving Early Detection of ASD in Community Systems

Wetherby et al. (Oct. 2015) Mobilizing community systems to tackle challenges of early detection of ASD, Oral Presentation at the DEC Conference, Atlanta, GA

Birth to 5: Watch Me Thrive!
Office of the Administration for Children and Families

Coordinated federal effort to help families and providers:

- Celebrate milestones.
- Promote universal screening.
- Identify possible delays & concerns early.
- Enhance developmental supports.

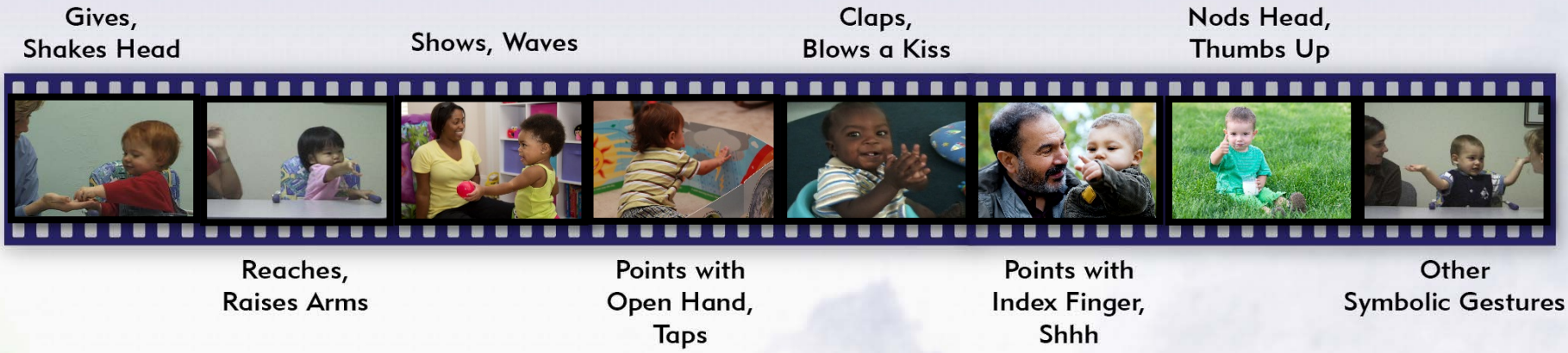
Learn the Signs. Act Early.

Are these milestones contributing to the solution or the problem?

9 Months	12 Months	18 Months
Social & Emotional		
May be afraid of strangers	Is shy or nervous with strangers	Likes to hand things to others as play
May be clingy with familiar adults	Cries when mom or dad leaves	May have temper tantrums
Has favorite toys	Has favorite things & people	May be afraid of strangers
Language		
Understands “no”	Responds to simple spoken requests	Says several single words
Makes a lot of different sounds	Uses simple gestures, like shaking head “no” or waving	Says and shakes head “no”
Copies sounds and gestures	Makes sounds with changes in tone	Points to show someone what he wants

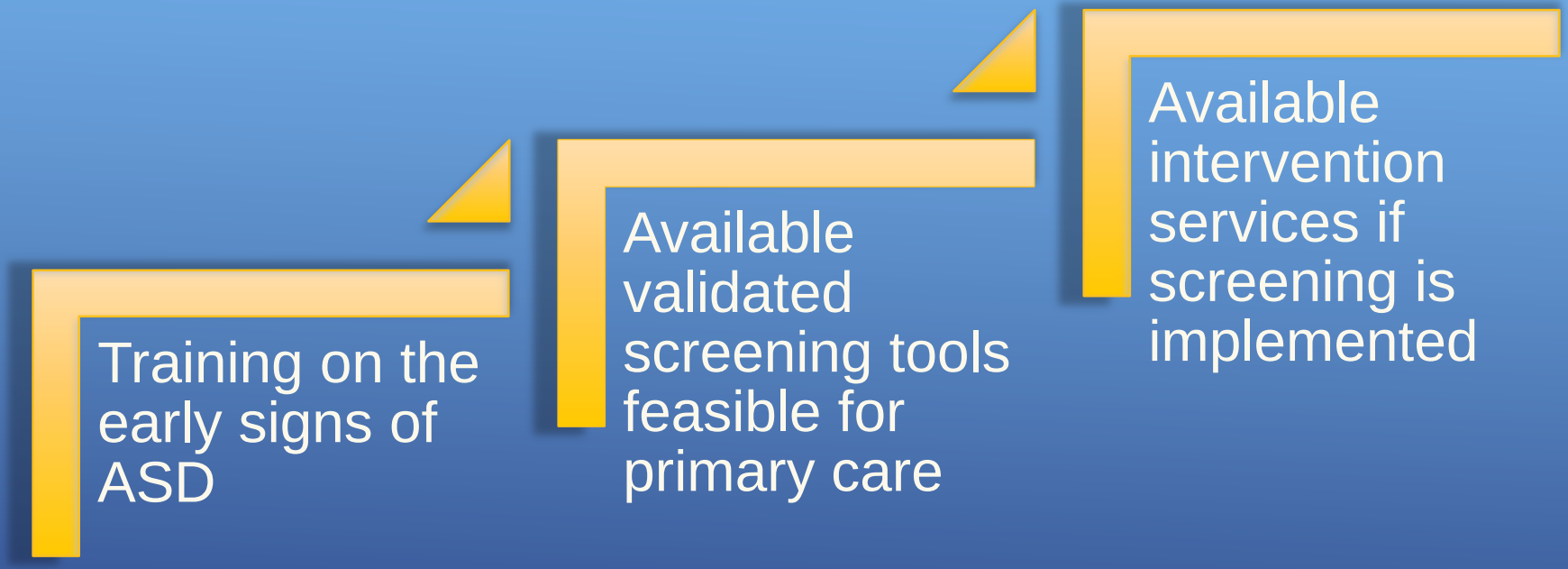
Development of gestures at 9 to 16 months predicts language 2 years later

(Caselli, Rinaldi, Stefanini, & Volterra, 2012; Rowe & Goldin-Meadow, 2009; Watt, Wetherby, & Shumway, 2006)



Children should use at least 16 gestures by 16 months.

Focus Groups with Professionals (n=41): Overcoming Barriers to Improving Early Detection of ASD in Community Systems

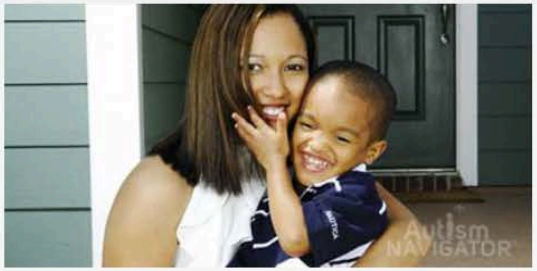


Wetherby et al. (Oct. 2015) Mobilizing community systems to tackle challenges of early detection of ASD, Oral Presentation at the DEC Conference, Atlanta, GA

Autism NAVIGATOR

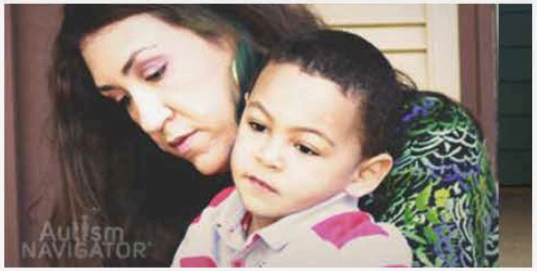
What Is Autism? About Family Resources Courses Contact Us

Autism Navigator is a unique collection of web-based tools and courses that uses extensive video footage to bridge the gap between science and community practice.



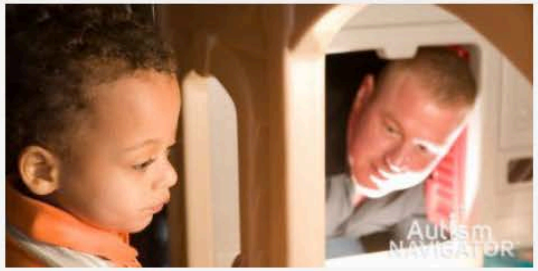
Family Resources

For parents, professionals, and anyone interested in learning about autism



Professional Courses

Learn about evidence-based practices in our professional development courses



Explore *About Autism in Toddlers*

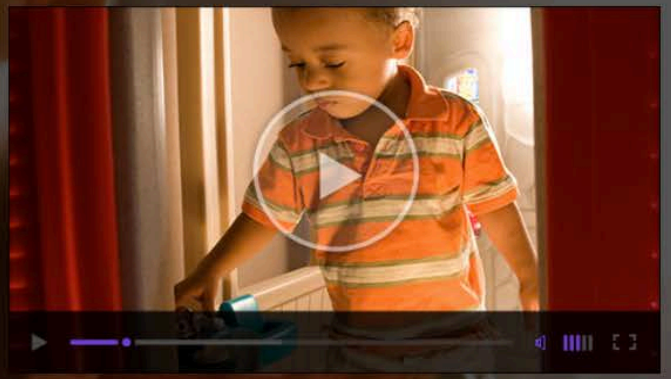
Watch unique side-by-side videos that show the early signs of autism in toddlers

Autism NAVIGATOR®

About Autism in Toddlers

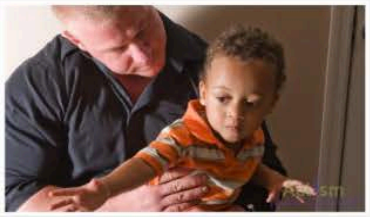
- Our first online course – FREE to the public
- For families, professionals, or anyone interested in learning about autism spectrum disorder (ASD)
- Video clips of over a dozen toddlers with ASD at 18-24 months of age

GET STARTED



WATCH PREVIEW

Courses for professionals, parents, and anyone interested in learning about autism.



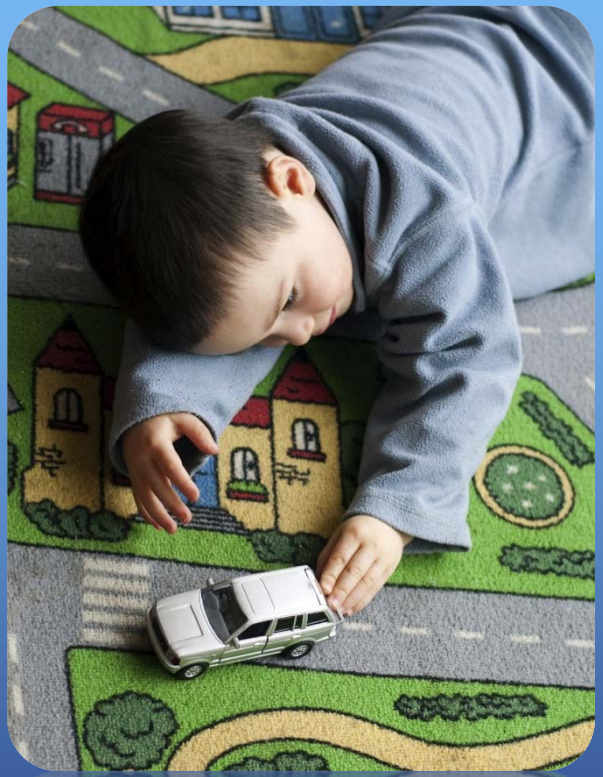
About Autism in Toddlers

Our first online course free to the public is for families, professionals, or anyone interested in learning about autism spectrum disorder (ASD). You will learn about the core diagnostic features and early signs of autism in toddlers, the critical importance of early detection and early intervention, and current information on prevalence and causes of autism. This self-paced course has video clips of over a dozen toddlers with ASD at 18-24 months of age. It takes about 2 hours to go through all of the slides and videos or spend a few minutes and visit again later.

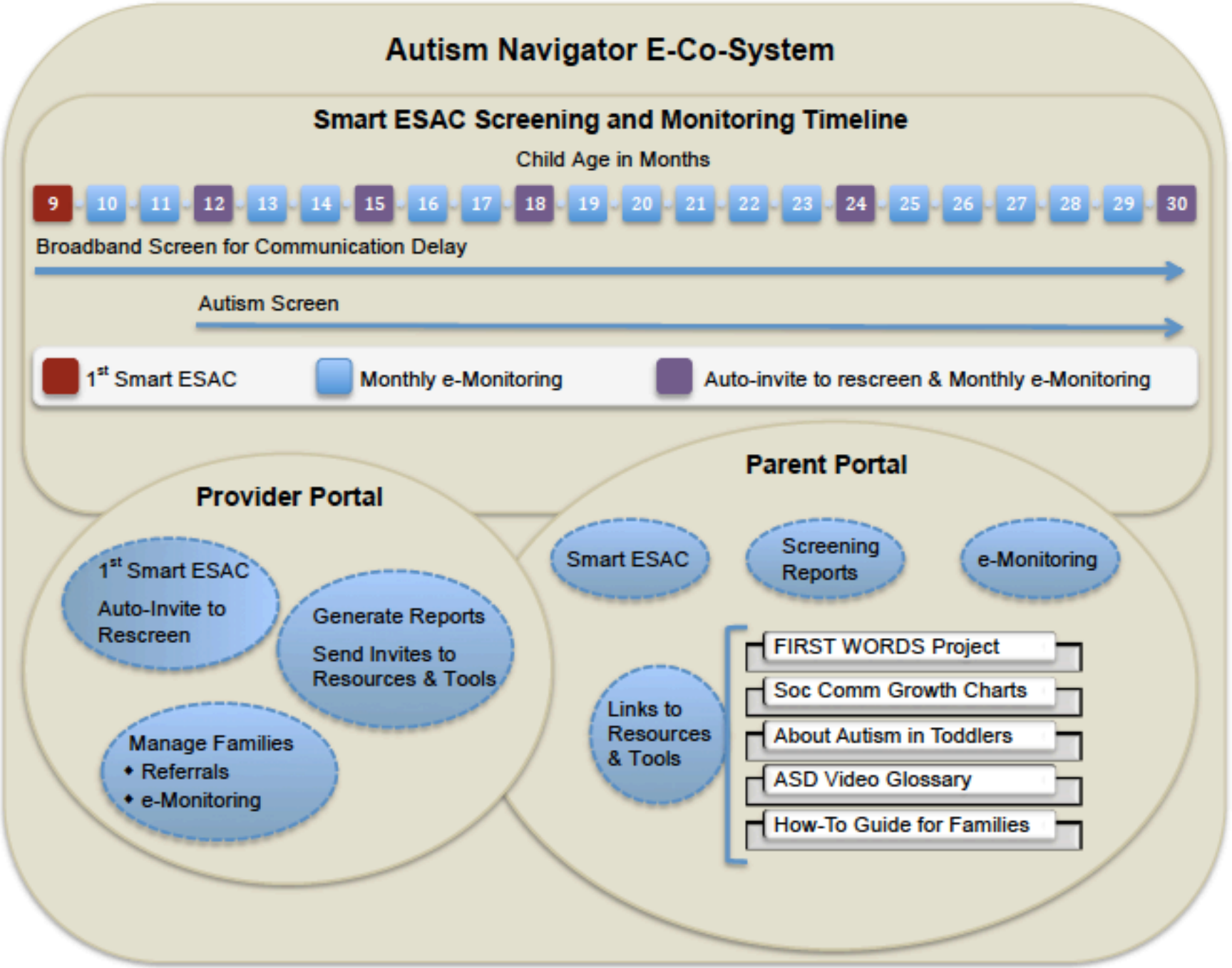
WATCH PREVIEW GET STARTED

Autism NAVIGATOR® for Primary Care

- Course Introduction
- 1. Core Diagnostic Features
- 2. Prevalence and Cause
- 3. Early Detection
- 4. Collaborating with Families
- 5. Screening & Referral
- 6. Early Intervention Basics



This 7-hour course launched in Summer, 2015.


Autism Navigator E-Co-System
Smart ESAC Screening and Monitoring Timeline
Child Age in Months
9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Broadband Screen for Communication Delay
Autism Screen
1st Smart ESAC
Monthly e-Monitoring
Auto-invite to rescreen & Monthly e-Monitoring
Provider Portal
1st Smart ESAC
Auto-Invite to Rescreen
Generate Reports
Send Invites to Resources & Tools
Manage Families
Referrals
e-Monitoring
Parent Portal
Smart ESAC
Screening Reports
e-Monitoring
Links to Resources & Tools
FIRST WORDS Project
Soc Comm Growth Charts
About Autism in Toddlers
ASD Video Glossary
How-To Guide for Families

Family Resources

A Seamless Path for Families

The Autism Navigator® is linked with a tiered system of online courses, tools, and resources to support families. Families are first invited for universal screening with the Smart Early Screening for Autism and Communication Disorders (ESAC) beginning at 9 months of age and to join a parent portal. This portal posts the screening report and sends invitations to the tiered system of supports for families based on the child's screening outcome. Families are invited to be re-screened every 3 to 6 months until 30 months of age. Following are the tiered supports for families:

1 16 Gestures by 16 Months & more

For all families—the 16 by 16™ series of Lookbooks to help families and others learn critical social communication skills that children should reach by 16 months to help their child learn to talk.

2 Social Communication Growth Charts

For all families—explore video clips to learn key social communication milestones that develop from 9 to 24 months and chart their child's social communication development.

3 About Autism in Toddlers

For families of children with a positive screen for autism—to learn about the early signs of autism with video clips of over a dozen toddlers with ASD at 18-24 months of age and see early intervention in action.

4 ASD Video Glossary

For families of children with a positive screen for autism who want more information—to see a library of hundreds of video clips illustrating diagnostic features and different interventions.

5 How-To Guide for Families

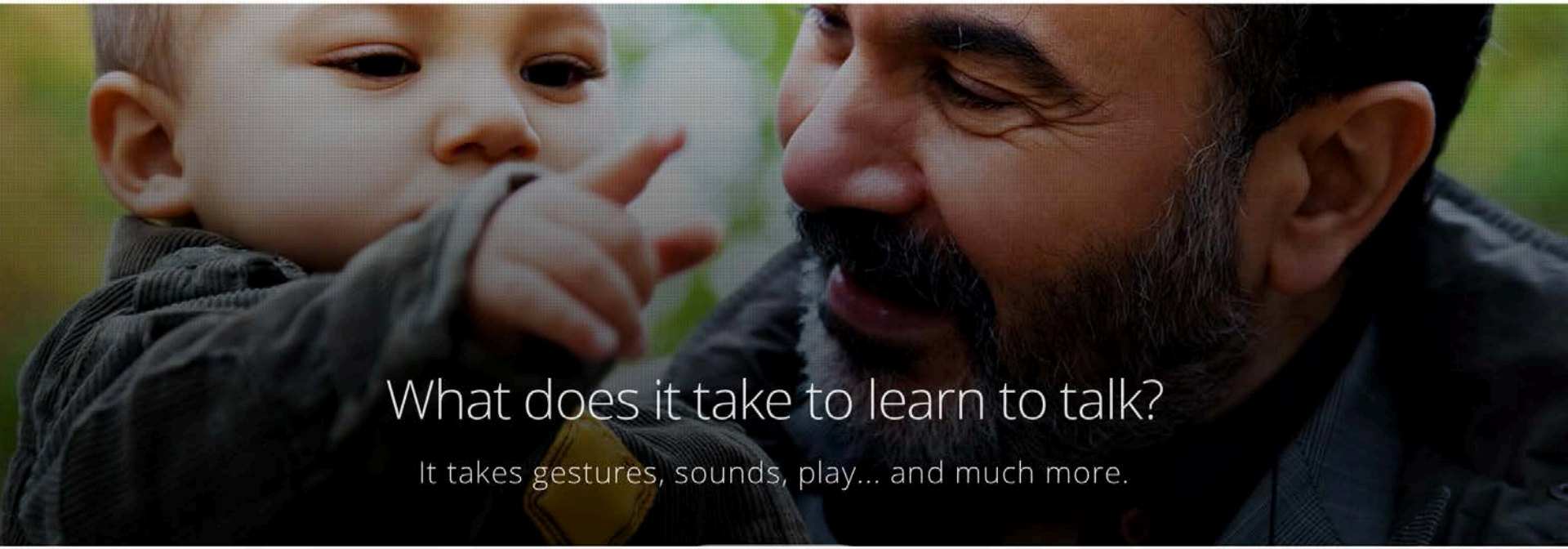
For families who suspect their child has ASD— to get started right away and learn intervention strategies to use in their everyday activities and support their child's learning and development.

Seamless Path for Families

For all families

FIRST WORDS PROJECT

Resources 16 by 16 Growth Charts About Get Involved Contact



Watch, Learn, and Spread the Word

Because the development of infants and toddlers is important to everybody.

www.FirstWordsProject.com

16 by 16™

Language Learning

16 Gestures by 16 Months

Imagination

16 Actions with Objects by 16 Months

Social Connectedness

16 Ideas to Communicate by 16 Months

Cooperation

16 Ways to Manage Emotions by 16 Months

Critical Thinking

16 Messages to Understand by 16 Months

16by16

10 MONTHS: REACH, RAISE ARMS

16 GESTURES BY 16 MONTHS

FIRST WORDS PROJECT


16by16
10 MONTHS: REACH, RAISE ARMS
then, with an open hand facing up, ...
16 GESTURES BY 16 MONTHS
FIRST WORDS PROJECT

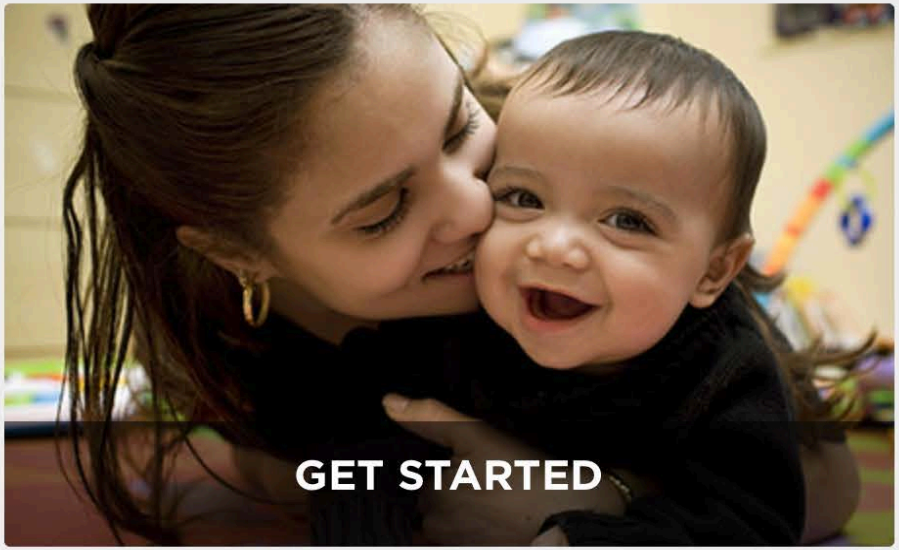

16by16
10 MONTHS: REACH, RAISE ARMS
...and finally, with their arms raised asking to be picked up.
16 GESTURES BY 16 MONTHS
FIRST WORDS PROJECT

SOCIAL COMMUNICATION™ GROWTH CHARTS

Home | About | Guided Tour | Get Started

Social Communication Growth Charts

Learn the milestones. Launch language early.



SOCIAL COMMUNICATION™ GROWTH CHARTS

Home About Guided Tour Get Started

Select Explore or Chart

EXPLORE

Learn the milestones.
Support your child's development.

Start Exploring

CHART

Watch your child grow.
Celebrate the small steps.

Start Charting

Seamless Path for Families

For all families

For families of children with a positive screen for autism

Autism Navigator is a unique collection of web-based tools and courses that uses extensive video footage to bridge the gap between science and community practice.

www.AutismNavigator.com

ASD PEDS Network Meeting

ASD Pediatric Early Detection, Engagement & Services Network

NIH National Institute of Mental Health

Services Research for Autism Spectrum Disorder across the Lifespan

Research on Early Identification and Linkage to Services for ASD (R01)

Carter, Alice S; Sheldrick, Radley
Addressing Systemic Health Disparities in Early ASD Identification & Treatment
University Of Massachusetts Boston

Feinberg, Emily
Early Identification & Service Linkage for Urban Children with Autism
Boston University Medical Campus

Pierce, Karen
Detection of ASD at the 1st Birthday as Standard Of Care: The Get SET Early Model
University of California San Diego

Stone, Wendy
A Screen-Refer-Treat (SRT) Model to Promote Earlier Access to ASD Intervention
University of Washington

Wetherby, Amy; Klin, Ami; Lord, Catherine; Newschaffer, Craig
Mobilizing Community Systems to Engage Families in Early ASD Detection and Services
Florida State University, Emory University, Weill Cornell Medical College, Drexel University

Meeting of the IACC

Afternoon Agenda

4:15	**Round Robin**
4:45	**Closing Remarks**
5:00	**Adjournment**

Next IACC Full Committee Meeting:

- Tuesday, April 19, 2016 – Building 31, NIH Campus, Bethesda, MD

Meeting of the IACC

Round Robin

Meeting of the IACC

Closing Remarks

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

Meeting of the IACC

Adjournment