

Autism as a Public Health Problem

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- ◆ Increasing* incidence
- ◆ Large morbidity burden
- ◆ Unknown cause
- ◆ Heightened public anxiety



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The autism “epidemic”



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Autism Diagnoses Double In California

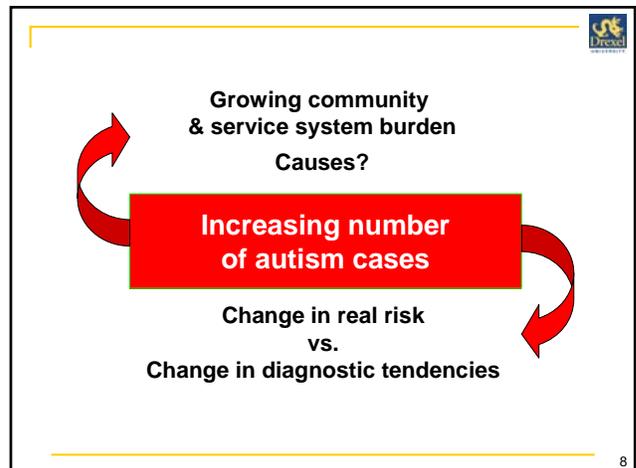
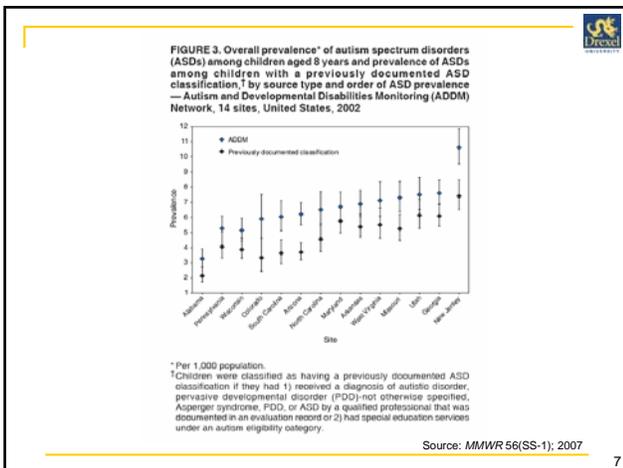
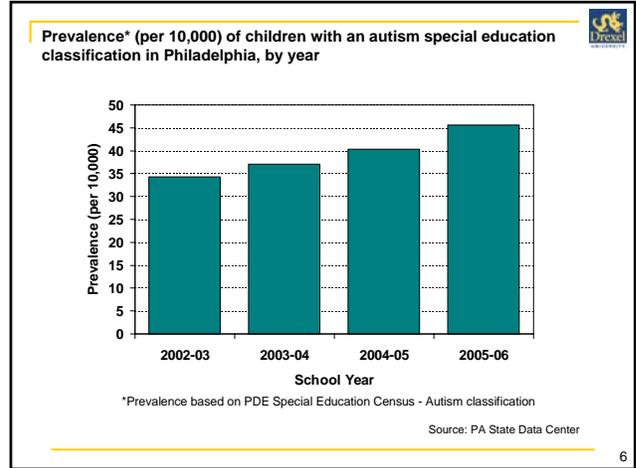
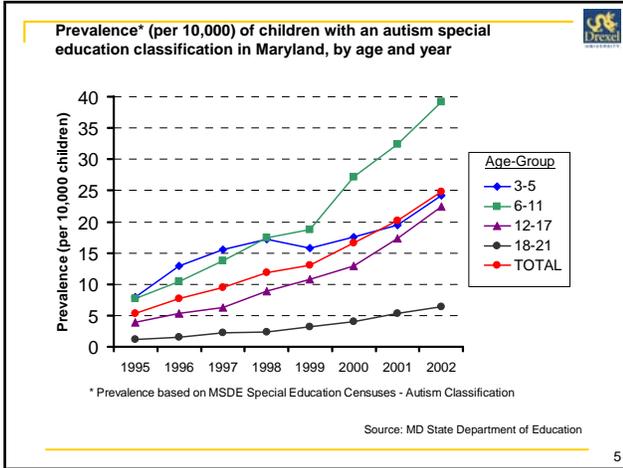
By SANDRA BLAKESLEE

Diagnoses of autism have nearly doubled in the last four years among children in California, state officials reported yesterday. They said they could not explain the increase.

New York Times, May 14 2003



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MEDICAL NEWS & PERSPECTIVES

"Epidemic" of Malignant Melanoma True Increase or Better Detection?

Lynne Lamberg

NEW ORLEANS—In 1930, an American's lifetime risk of developing invasive malignant melanoma (MM) was estimated to be one in 1500. Today, the estimated risk is 1 in 68.

An estimated 53000 Americans will be diagnosed as having invasive MM this year, and 7400 Americans are expected to die of this disease, according to the American Cancer Society (ACS). The ACS reports that MM is the fifth most common cancer in men and sixth most common in women. These data

specific antigen tests. No clinical test exists to detect MM in a preclinical state.

The incidence of thin invasive lesions (<0.1 mm) is increasing faster than that of thick ones (>1.0 mm) said Rigel, a past AAD president. This finding, he said, reflects earlier detection by physicians and greater awareness of warning signs of skin cancers by the public.

There have been no significant changes in histological criteria for the diagnosis of MM in recent years, Rigel said. A review of nearly 2700 pig-

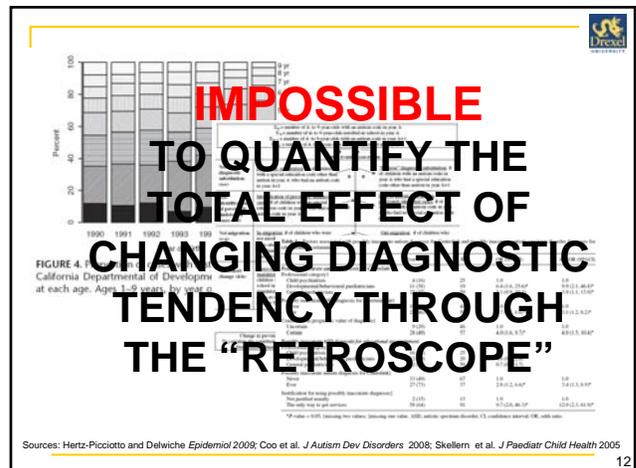
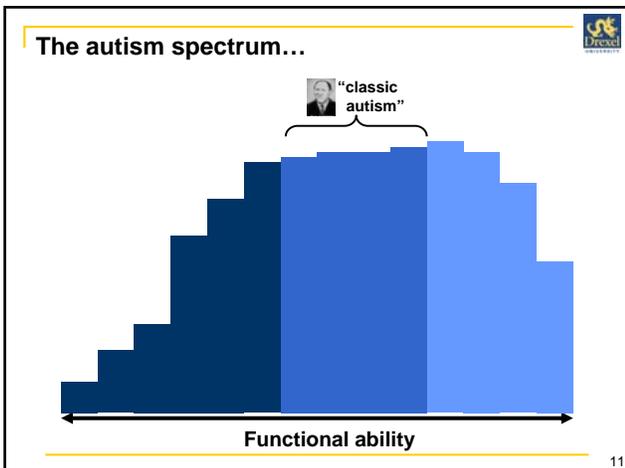
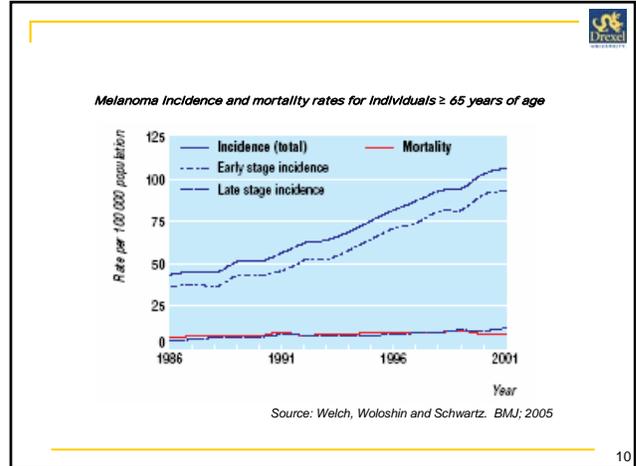
The rise, she suggested, may at least in part reflect longer life expectancy, particularly in men. Efforts to detect MM earlier also are paying off, she said, with the identification of more and thinner lesions. Thin MMs may have a long latent period, she said, and may not reduce longevity.

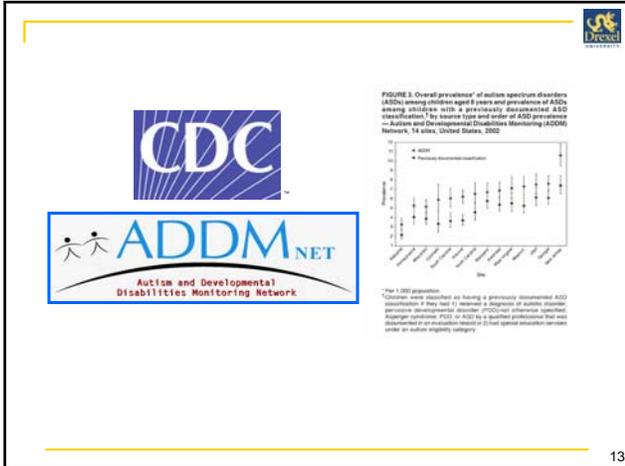
Is it true that for every MM that is removed, she asked, a life is saved? Her answer: "Perhaps."

"We can't say that nonfatal MMs exist," Rigel countered. Even thin lesions, he said, have a 2% to 3% mortality rate.

Source: Lamberg. JAMA; 2002

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Autism public health burden and system challenges

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- ### Public health burden of autism
- ♦ 2nd most common serious developmental disability
 - ♦ Lifelong impairment*
 - ♦ \$35 billion annual costs (direct and indirect)
 - ♦ 70 new cases diagnosed per day

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- ### Challenge 1: detect and diagnose early
-
- ♦ Improve general developmental screening *plus* autism-specific screening
 - ♦ Time / reimbursement / false positives
 - ♦ Standardized diagnostic tools have advanced research but are still impractical in the clinic
 - ♦ Develop alternate diagnostic “pathways”

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Challenge 2: increase access to early intervention



Early, behaviorally-based intervention is critical!

- As early as possible
- Intense (min 25 hrs wk)
- Systematic, planned, developmentally focused
- Individual attention
- Must focus on:
Communication Social cognition
Behavior management Develop.

Oxytocin vasopressin → Activation of reward system
 - Amygdala
 - Prefrontal cortex

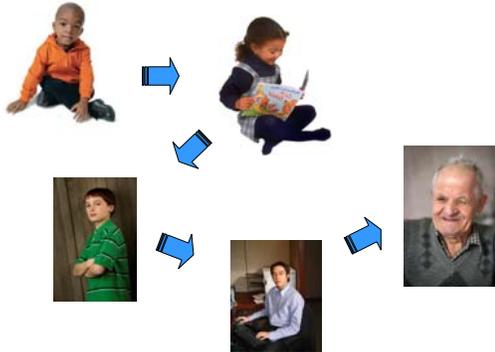
Dopamine reward system → Integration of limbic, temporal, frontal and cerebral regions
 - Joint attention
 - Social Imitation

Dawson's social motivation theory

ENRICHED ENVIRONMENT THROUGH BEHAVIORAL INTERVENTION

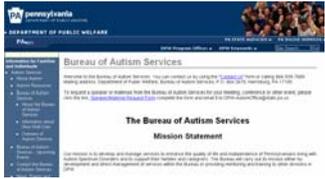
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Challenge 3: improve services through the lifespan



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Innovation in Pennsylvania



PA Autism Service Education Resources and Treatment (ASERT) Centers



PA Autism Insurance Act (ACT 62)

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Questions of cause...

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Table 3. Distribution and AOR* (95% CI) for autism risk by quartile^b of hazardous air pollutant groups.

Group ^c	HAP group level			
	First and second quartile no. of cases/controls Referent group	Third quartile no. of cases/controls AOR (95% CI)	Fourth quartile no. of cases/controls AOR (95% CI)	
Mechanistic				
Endocrine disruptors	128/228	88/173	70/156	
Developmental toxicants	128/219	133 (0.84-1.98)	129 (0.88-1.89)	1.71 (1.02-2.87)**
Structural				
Aromatic solvent				
Chlorinated solvnt				
Metals				
Phenolics	0.77 (0.27-2.24)	1.34 (0.50-3.59)	2.25 (0.99-5.16)**	
Child	1.41 (0.75-2.64)	1.11 (0.61-2.03)	1.71 (1.02-2.87)**	
DMs				
Phenolics	0.79 (0.31-1.96)	1.27 (0.52-3.04)	2.19 (1.09-4.50)**	
Child	1.54 (0.85-2.76)	1.10 (0.62-1.94)	1.52 (0.94-2.45)*	
Metals				
Phenolics	0.78			
Child	1.02			

Table 5. Adjusted^d ORs (95% CIs) for syndrome scores in the clinical (CU) or borderline clinical (BU) range on the CBCL at 24 months of age for DAPs primary metabolites.

CBCL	Attention (OR) ^e				ADHD (OR) ^e				FDD (OR) ^e			
	Phenolics	Child	DMs	Metals	Phenolics	Child	DMs	Metals	Phenolics	Child	DMs	Metals
CU	0.77 (0.27-2.24)	1.41 (0.75-2.64)	0.79 (0.31-1.96)	1.54 (0.85-2.76)	1.34 (0.50-3.59)	1.11 (0.61-2.03)	1.27 (0.52-3.04)	1.10 (0.62-1.94)	2.25 (0.99-5.16)**	1.71 (1.02-2.87)**	2.19 (1.09-4.50)**	1.52 (0.94-2.45)*
BU	0.78	1.02	0.78	1.02	0.78	1.02	0.78	1.02	0.78	1.02	0.78	1.02

Table 3. Adjusted OR^a (95% CI) for ASD among children born in selected California counties during 1986-1996, by nearest quartile of organochlorine pesticides applied within 100 m of residence during various periods of gestation.^b

Nearest quartile ^c of pesticide applied (inference = 1)	Normal (n = 10,323)		CNS (n = 40)		Gestation (n = 114)		Postnatal (n = 32)	
	0-100 days pre-fertilization	101-200 days pre-fertilization	0-100 days pre-fertilization	101-200 days pre-fertilization	0-100 days gestation	101-200 days gestation	0-100 days postnatal	101-200 days postnatal
First	1.0 (0.1-1.9)	0.6 (0.1-1.3)	0.6 (0.1-1.3)	1.2 (0.4-3.1)	0.6 (0.1-1.3)	1.2 (0.4-3.1)	0.6 (0.1-1.3)	1.2 (0.4-3.1)
Second	1.2 (0.2-6.8)	1.8 (0.4-7.1)	1.8 (0.4-7.1)	0.6 (0.1-1.3)	0.6 (0.1-1.3)	1.2 (0.4-3.1)	0.6 (0.1-1.3)	1.2 (0.4-3.1)
Third	2.6 (0.6-10.8)	2.4 (0.7-8.2)	2.4 (0.7-8.2)	1.8 (0.5-6.2)	1.8 (0.5-6.2)	2.4 (0.7-8.2)	2.6 (0.6-10.8)	2.4 (0.7-8.2)
Fourth	3.1 (1.0-12.9)	4.2 (1.7-10.9) ^d	4.2 (1.7-10.9) ^d	1.8 (1.0-3.2)	1.8 (1.0-3.2)	4.2 (1.7-10.9) ^d	3.1 (1.0-12.9)	4.2 (1.7-10.9) ^d

Sources: Windham et al *Env Health Persp* 2006; Eskenazi et al. *Env Health Persp* 2007; Roberts et al *Env Health Persp* 2007

Immunization and autism

Early report

Bealymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

JAMA. 1998;279:1157-1161. doi:10.1001/jama.279.13.1157.

Abstract

Background: We investigated a consecutive series of children with chronic enterocolitis and pervasive developmental disorder.

Methods: 12 children (mean age 11 years [range 3-16]) had been referred to a pediatric gastroenterology unit with a history of chronic inflammation limited to the ileum and sigmoid colon, including together with diarrhea and abdominal pain. Children underwent gastrointestinal, histologic, and developmental assessment and review of developmental events, immunizations and timing, and timing of onset of symptoms.

Results: All children had ileocolitis and had autoimmune enteropathy (AIE), and had autism spectrum disorder (ASD).

Conclusions: We describe the clinical features and pathogenesis of AIE in children with ASD.

Keywords: Autism spectrum disorder; enterocolitis; immunization; pervasive developmental disorder.

Introduction

We are aware of children who, after a period of apparent normality, but acquired skills, including communication, intellectual skills, and motor skills, and who, in some cases, had diarrhea. We describe the clinical features and pathogenesis of these children.

Patients and methods

12 children, consecutively referred to the department of pediatric gastroenterology with a history of chronic inflammatory ileocolitis, additional symptoms of autism spectrum disorder, and timing of onset of symptoms, were investigated. All children were referred to the unit in 1998, and were followed up to 2007.

Table. Rate Ratio of Autism and Other Autism Spectrum Disorders Comparing Children Vaccinated With a Thimerosal-Containing Vaccine to Children Vaccinated With a Thimerosal-Free Formulation of the Same Vaccine

Vaccine	Person-Years at Risk	Autism		Other Autism Spectrum Disorders	
		No. of Cases	RR (95% CI) ^a	No. of Cases	RR (95% CI) ^a
Vaccinations					
All thimerosal-free	1 080 159	303	1.00	430	1.00
Any containing thimerosal	1 220 096	104	0.85 (0.65-1.10)	321	1.12 (0.88-1.43)
Cases of thimerosal-containing vaccine					
None	1 080 159	303	1.00	430	1.00
1 dose (25 µg ethylmercury)	103 020	16	0.99 (0.59-1.68)	40	0.96 (0.67-1.38)
2 doses (50 µg ethylmercury)	441 970	33	0.71 (0.48-1.08)	100	1.25 (0.92-1.68)
3 doses (75 µg ethylmercury)	855 113	55	0.96 (0.63-1.48)	151	1.11 (0.83-1.48)
Total thimerosal in 25 µg ethylmercury	0.96 (0.90-1.00)	0.98 (0.90-1.00)	1.03 (0.97-1.08)	1.03 (0.98-1.08)	

Figure 1: Prevalence of Autism Spectrum Disorders (ASD) by Year of Birth (1987-1998).

Figure 2: Ethylmercury Exposure (µg/kg body weight) by Year of Birth (1987-1998).

Sources: Hviid et al. *JAMA* (2003); Schecter and Grether *Arch Gen Psych* (2008)

The New York Times

Court Says Vaccine Not to Blame for Autism

By David G. Greenberg, Staff Writer

In a blow to the movement arguing that vaccines lead to autism, a special court ruled on Thursday against three families seeking compensation from the federal vaccine injury fund.

Both sides in the debate have been awaiting decisions in these test cases since hearings began in 2007; more than 5,000 similar claims have been filed.

In the three cases, each decided by a judge called a special master, the families had not shown that their children's autism was brought on by vaccine — either the measles, mumps and rubella combination, with thimerosal, a mercury-based preservative that was a childhood vaccine until 2001.

In a case pitting the family of Michelle Cedillo, a severely autistic child, Department of Health and Human Services, the judge ruled that the CDC demonstrate that thimerosal-containing vaccine can contribute to autism.

Statement by Autism Speaks Regarding February 12 Vaccine Court Decision

Autism Speaks

Today the National Vaccine Injury Compensation Program ruled that the combination MMR vaccine — with and without the preservative thimerosal — did not contribute to three particular children's autism. These rulings are limited, and do not mitigate the need for further scientific investigation.

The causes of autism remain poorly understood. Autism Speaks funds an aggressive program of research on the causes and best treatments for autism. We will continue to support substantive research that addresses unanswered questions about whether certain subgroups of individuals with particular underlying medical or genetic conditions may be more vulnerable to adverse effects of vaccines. While large scale studies have not shown a link between vaccines and autism, there are lingering legitimate questions about the safety of vaccines that must be addressed. Our families deserve nothing less than an exhaustive search using a rigorous scientific approach.

The millions of Americans affected by autism continue to seek answers to a wide array of critical questions, from what genetic and environmental factors may contribute to autism to how we can develop better treatments and effective methods for early diagnosis. Their medical struggles and frustrations continue, as they fight for insurance coverage, services and access to education, while also bearing tremendous financial and emotional burdens.

SPECIAL ARTICLE

Vaccine Refusal, Mandatory Immunization, and the Risks of Vaccine-Preventable Diseases

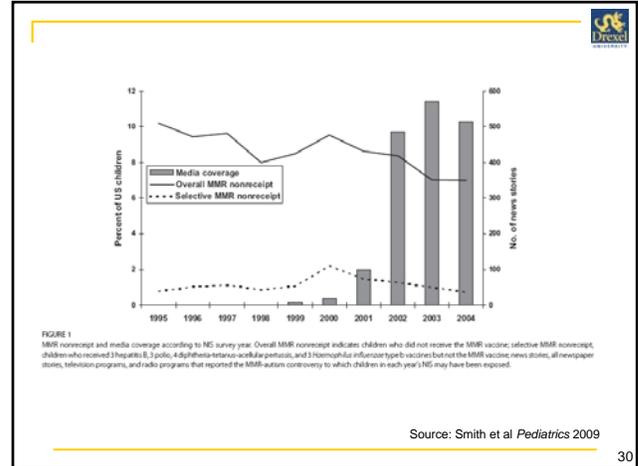
Saad B. Omer, M.B., B.S., Ph.D., M.P.H., Daniel A. Salmon, Ph.D., M.P.H.,
Walter A. Orenstein, M.D., M. Patricia deHart, Sc.D., and Neal Halsey, M.D.

ABSTRACT

Vaccines are among the most effective prevention tools available to clinicians. However, the success of an immunization program depends on high rates of acceptance and coverage. There is evidence of an increase in vaccine refusal in the United States and of geographic clustering of refusals that results in outbreaks. Children with exemptions from school immunization requirements (a measure of vaccine refusal) are at increased risk for measles and pertussis and can infect others who are too young to be vaccinated, cannot be vaccinated for medical reasons, or were vaccinated but did not have a sufficient immunologic response. Clinicians can play a crucial role in parental decision making. Health care providers are cited as the most frequent source of immunization information by parents, including parents of unvaccinated children. Although some clinicians have discontinued or have considered discontinuing their provider relationship with patients who refuse vaccines, the American Academy of Pediatrics Committee on Bioethics advises against this and recommends that clinicians address vaccine refusal by respectfully listening to parental concerns and discussing the risks of nonvaccination.

Source: *NEJM* May 2009

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Next steps exploring autism risk factors...

- Larger studies to date capitalize on existing data systems (Scandinavian registries, Kaiser Permanente...)
- "First wave" of large studies (case-control) with primary data collection combining interview data, medical record data, genetics data, other biomarkers nearing completion...



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UCDavis NIEHS

- Next "wave"?
 - Case-only designs / case-parent trio designs
 - International comparisons
 - Designs focusing on maternal genetic effects
 - Large birth cohorts (e.g., NCS, Norwegian cohort)
 - **Enriched risk cohort designs**

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EARLI

Early Autism Risk Longitudinal Investigation



- One of 11 NIH Autism Centers of Excellence
- EARLI involves and administrative core, four field sites, data coordinating center, central receiving lab and biosample repository
- Collaborating institutions include: Drexel, CHOP, University of Pennsylvania, Johns Hopkins, Kennedy Krieger Institute, UC Davis MIND Institute, Kaiser Permanente

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EARLI Prospective data collection plan

Pre-pregnancy follow-up

DELIVERY

- Medical records
- Biological samples

Sibling @ 36 mos

Eligibility interview

PREGNANCY Mom

- Medical records
- Self-report
- Biological samples

Proband

- Medical records
- Behavioral assessments
- Physical examinations
- Biological samples

Home

- Environmental samples
- Environmental surveys

POST-PARTUM / EARLY CHILDHOOD Mom

- Biological samples

Sibling

- Medical records
- Behavioral assessments
- Physical examinations
- Biological samples
- Maternal report

Home

- Environmental samples
- Environmental surveys

- Multiple mode exposure data collection on several key domains
- Collection in multiple exposure windows (potential critical periods)
- Comprehensive outcome assessment (dichotomous, continuous, markers for etiologic heterogeneity)

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EARLI Example exposure assessment options

Infection

- Maternal blood in pregnancy (3-4 samples): Ig, PCR, CRP
- Maternal urine in pregnancy: PCR
- Symptoms in pregnancy (diary report)
- Placenta: histology, immunohistochemistry
- OB and L&D medical record
- Newborn heelstick: Ig
- Cord blood: Ig, PCR, CRP
- Breast milk: Ig
- Sibling blood (2 samples)
- Sibling urine (2 samples)
- Sibling symptom diary
- Pediatric medical record

Organophosphates

- Maternal urine in pregnancy: (3-4 samples): OP metabolites
- Housing characteristics – pregnancy
- Household dust samples
- Questionnaire – insecticide exposure in pregnancy; organic vs. nonorganic fruit and veg
- Meconium: OP metabolites
- Chord blood: chlorpyrifos levels
- Sibling urine (2 samples)
- Questionnaire – insecticide use postnatally; organic vs. nonorganic fruit and veg
- Housing characteristics – postnatal
- Household dust sample - postnatal

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www.earlistudy.org

EARLI Early Autism Risk Longitudinal Investigation
Finding Clues About Autism with Growing Families

Brain development begins very early – we need to study babies before they're born.

Benefits of Participation

Welcome to EARLI

EARLI is a network of research sites that will enroll and follow 1,200 mothers of children with autism at the start of another pregnancy and document the system child's development through three years of age. The EARLI study will examine possible environmental risk factors for autism and study whether there is any interplay between environmental factors and genetic susceptibility.

According to the Centers for Disease Control and Prevention, approximately 1 in every 150 children has an Autism Spectrum Disorder (ASD). ASD is the fastest growing developmental disability in the country, however, little is known about what causes it. The EARLI study is an important research study that will change that. If

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THANK YOU!

Any questions, or for a pdf copy of this presentation, you can reach me at:

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