The Epidemiology of Autism: Investigating Perinatal Risk Factors

Lisa Croen, PhD

Drexel Autism and Public Health Lecture, March 27 2019

Overview of Presentation

- What is epidemiology
- Epidemiology of autism
- Immune function and autism
- Future directions

What IS an Epidemiologist Anyway?

We don’t study bugs!

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Epidemiology is…

- The study of patterns of health and illness **at the population level**
- The identification of risk factors for disease
- It informs public health prevention strategies
- Ultimately leads to optimal treatment approaches **at the individual level**

How to Be an Epidemiologist in Three Easy Steps

Step 1: Define

- What is it?

Step 2: Describe

- How many people are affected?
- Who is affected?
- Where does it occur?
- When does it occur?

Step 3: Analyze

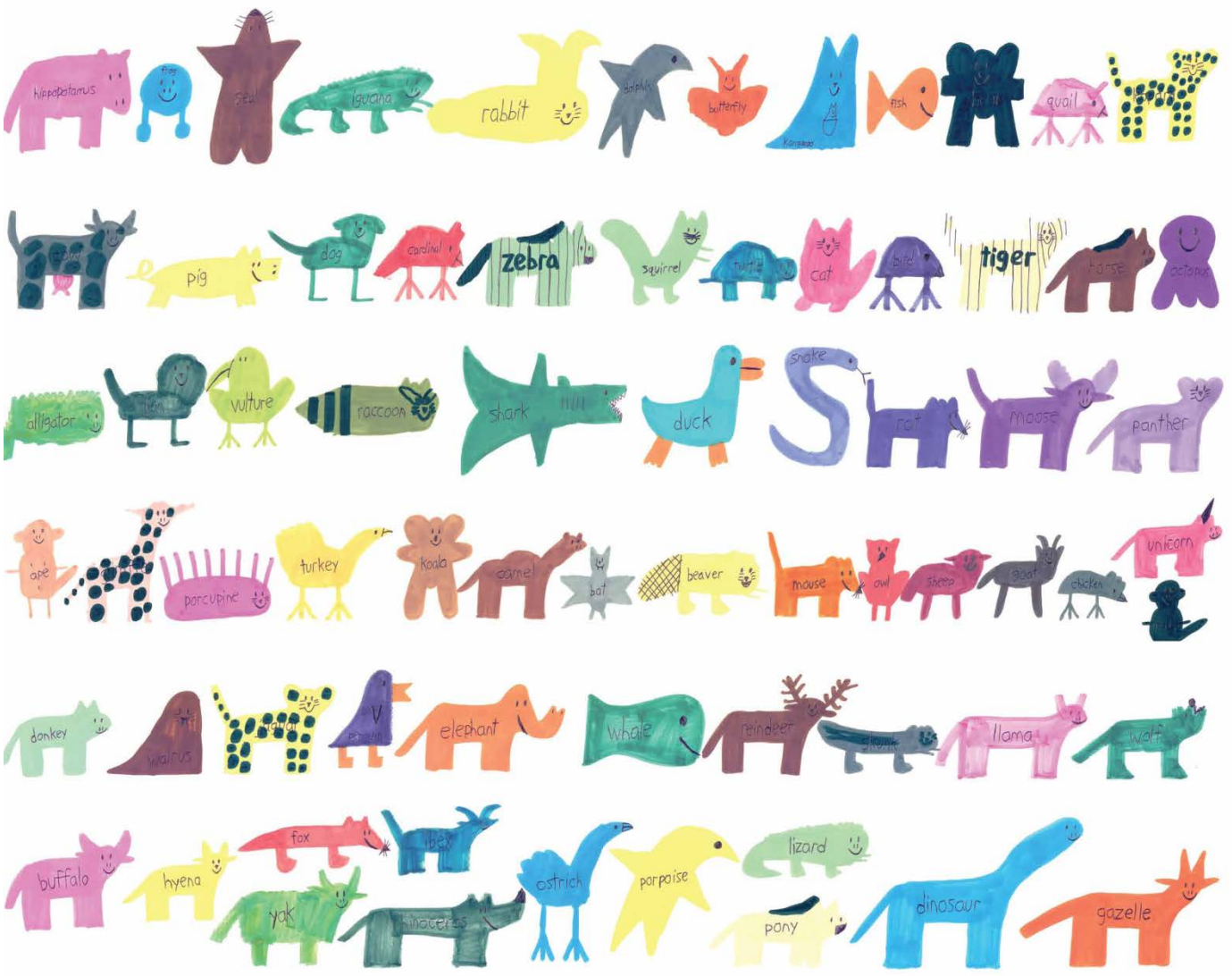
- Why does it happen?
- What are the risk factors? causes?

Step 1: Define

What is autism?

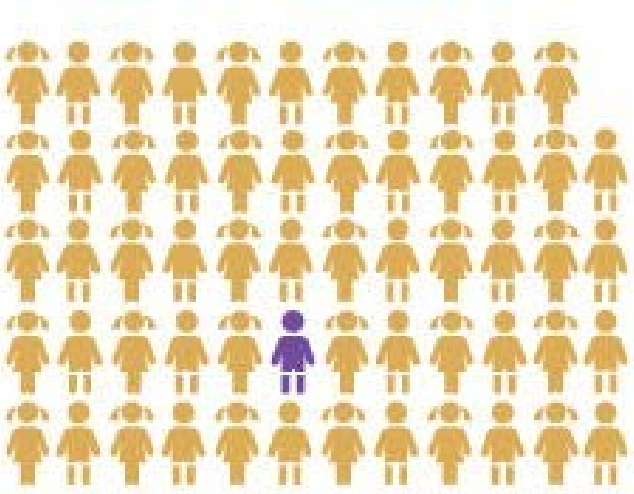
- Persistent deficits in social communication and social interaction across multiple contexts
- Restricted, repetitive patterns of behavior, interests, or activities
- Symptoms must be present in the early developmental period
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
- These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

“Autisms”



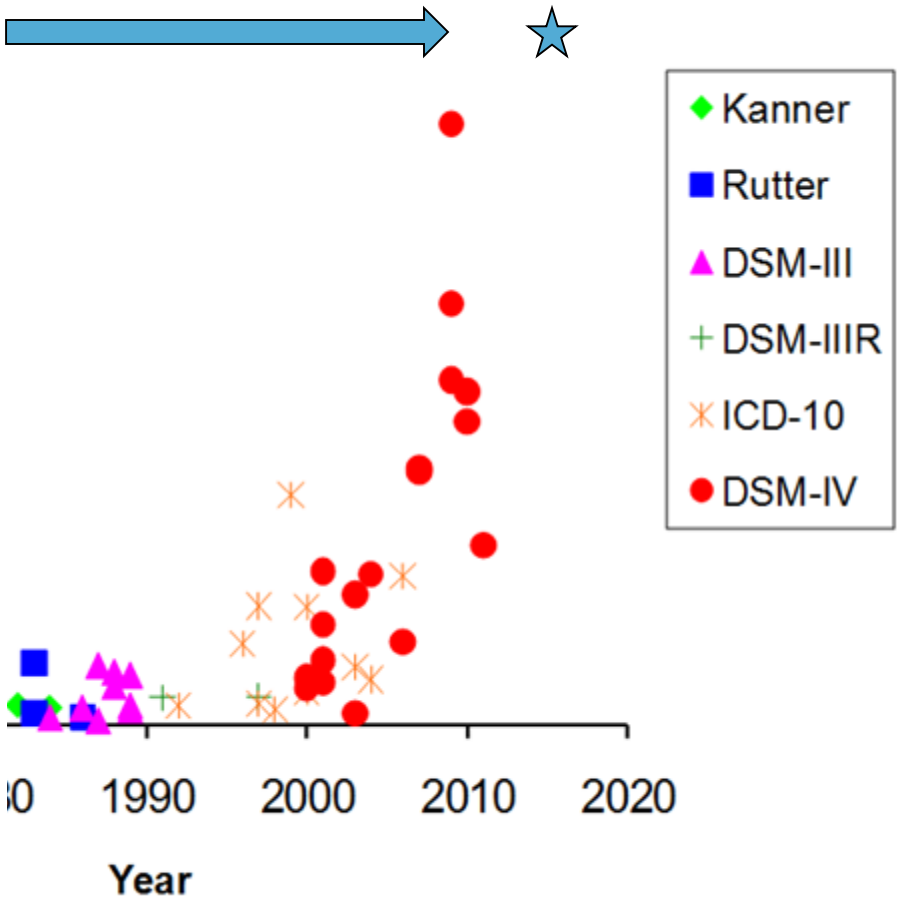
Step 2: Describe

Autism Spectrum Disorders (ASDs)



1 in 59

children living in ADDM sites are identified with ASD



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Step 3: Analyze

Investigating relationship between

Exposure and Outcome

?

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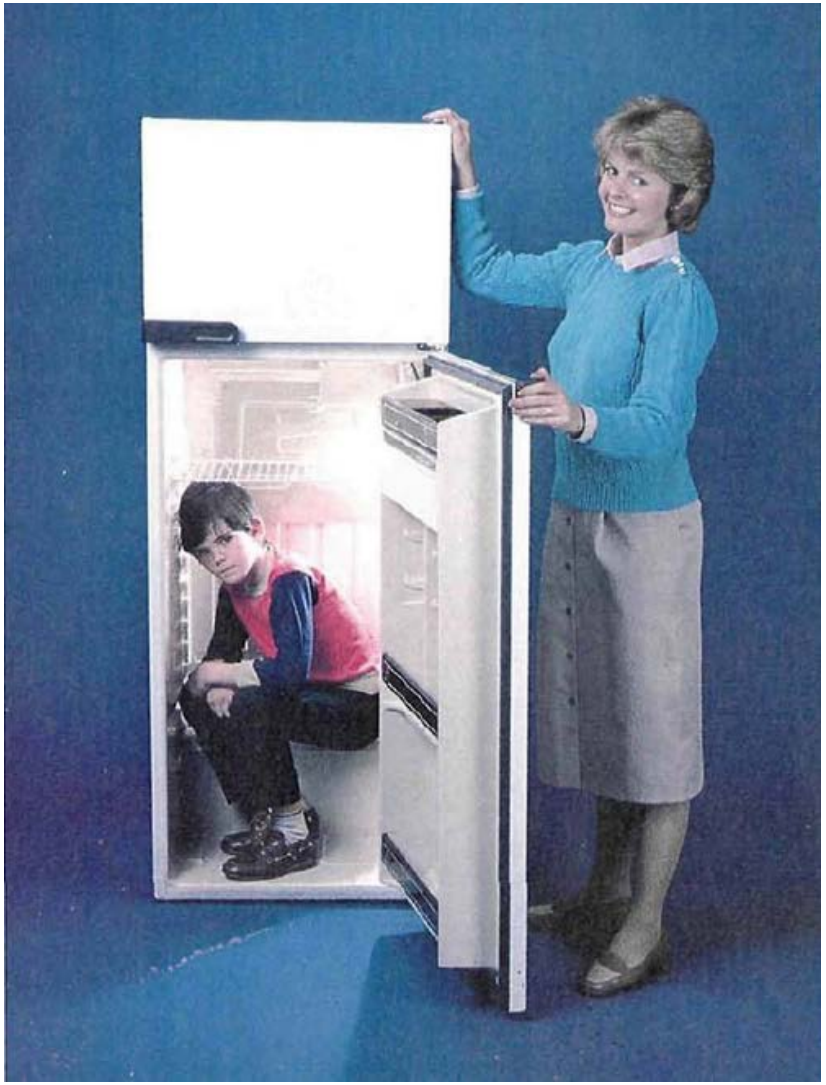
Refrigerator Mothers



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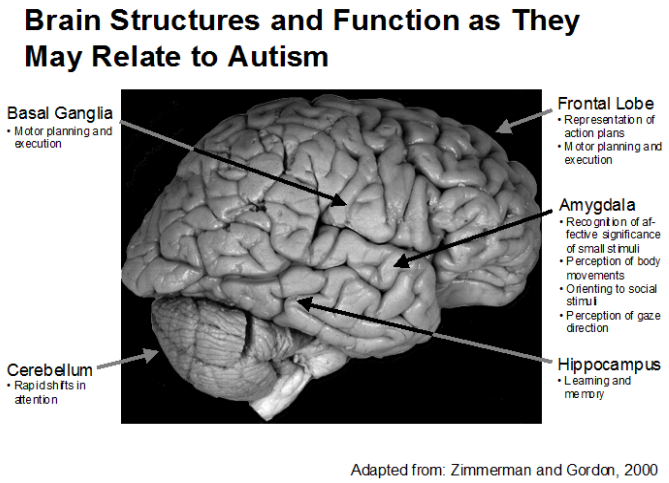
Prenatal Origins of Autism



Adapted from: Zimmerman and Gordon, 2000

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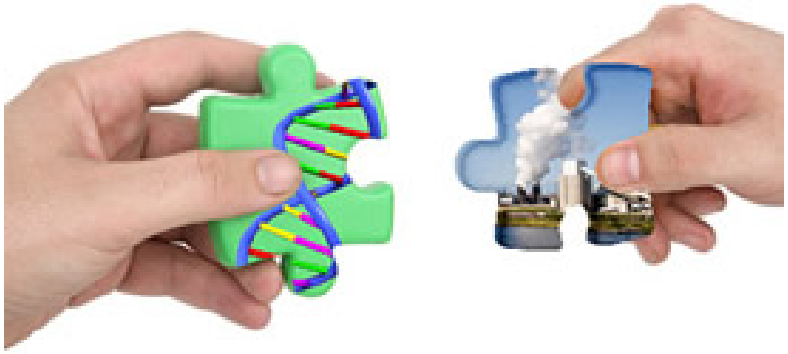
Autism Etiology: Genes And Environment



- Combination of genetic and environmental factors
- Critical exposure window is very early in development
- Different clinical subgroups likely have different risk factor profiles

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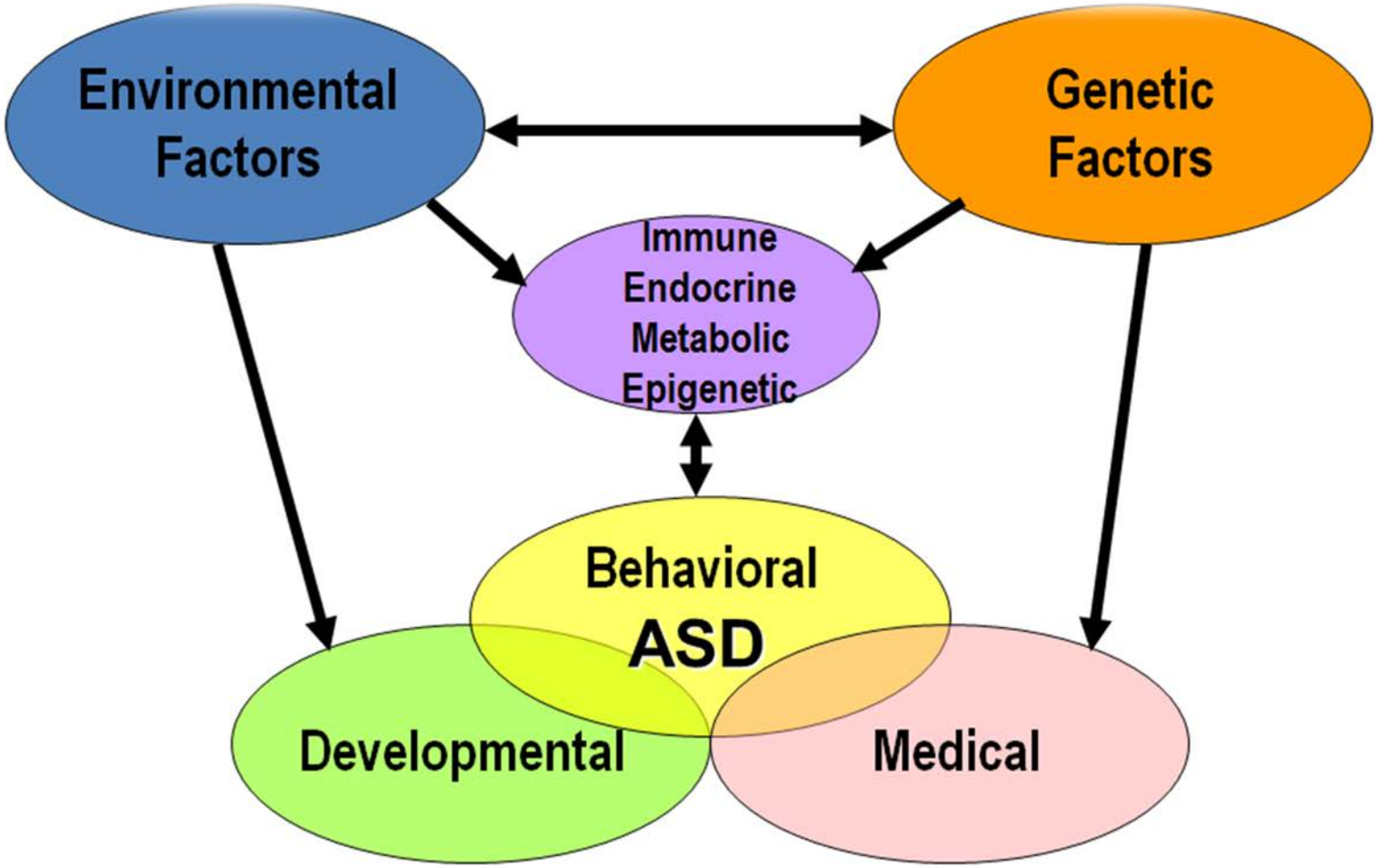
Conceptual Model of Autism Etiology



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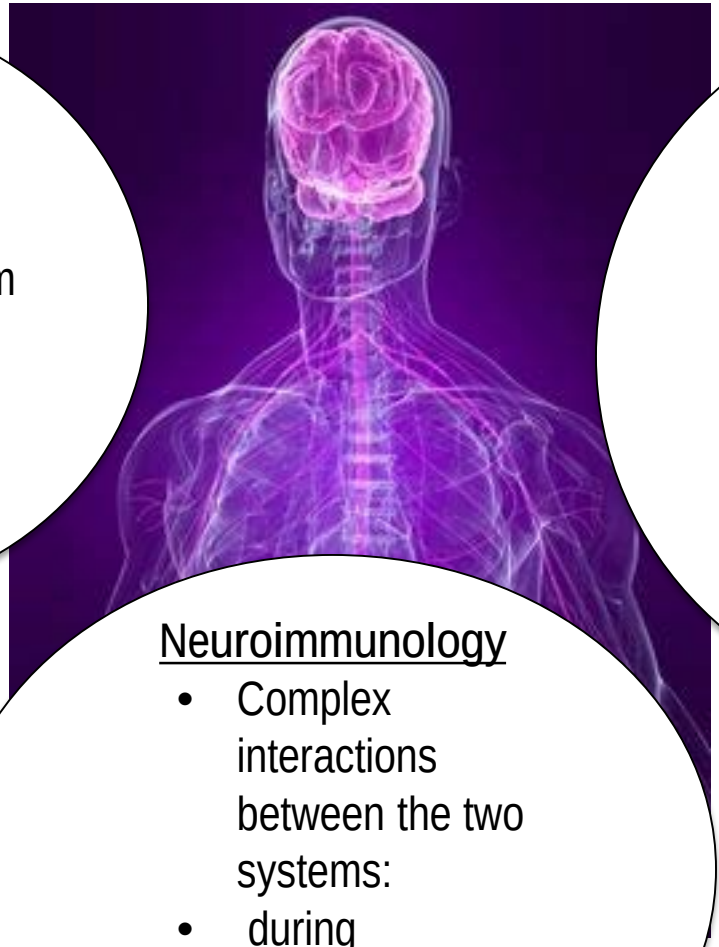
The Immune and Nervous Systems



Immune System

- Body's natural defense mechanism
- Detection of wide variety of foreign agents

Nervous System

- Transmit signals between different regions of the body
- Interactions between complex neural pathways
- CNS: brain and spinal cord
- PNS: sensory neurons

Neuroimmunology

- Complex interactions between the two systems:
- during homeostasis
- response to injury
- development

Key factors

- Cytokines/chemokines
- Immune signaling pathways
- Antibodies

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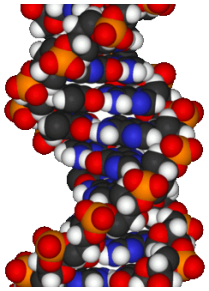
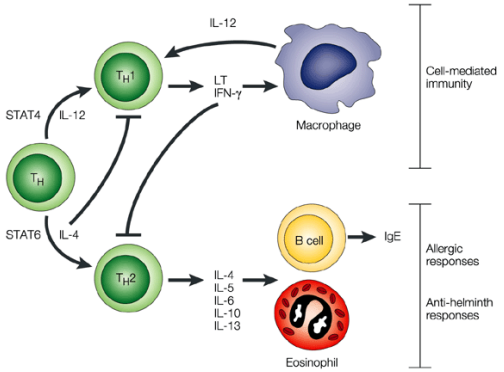
Immune Function in Autism

- Genes that regulate immune response
- Abnormal immune markers in peripheral blood of children with ASD
- Neuroglial activation and neuroinflammation in brain and CSF
- Infection, asthma, allergies in children with autism





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Are immune changes…

OR

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Maternal Immune Function

Postnatal Period

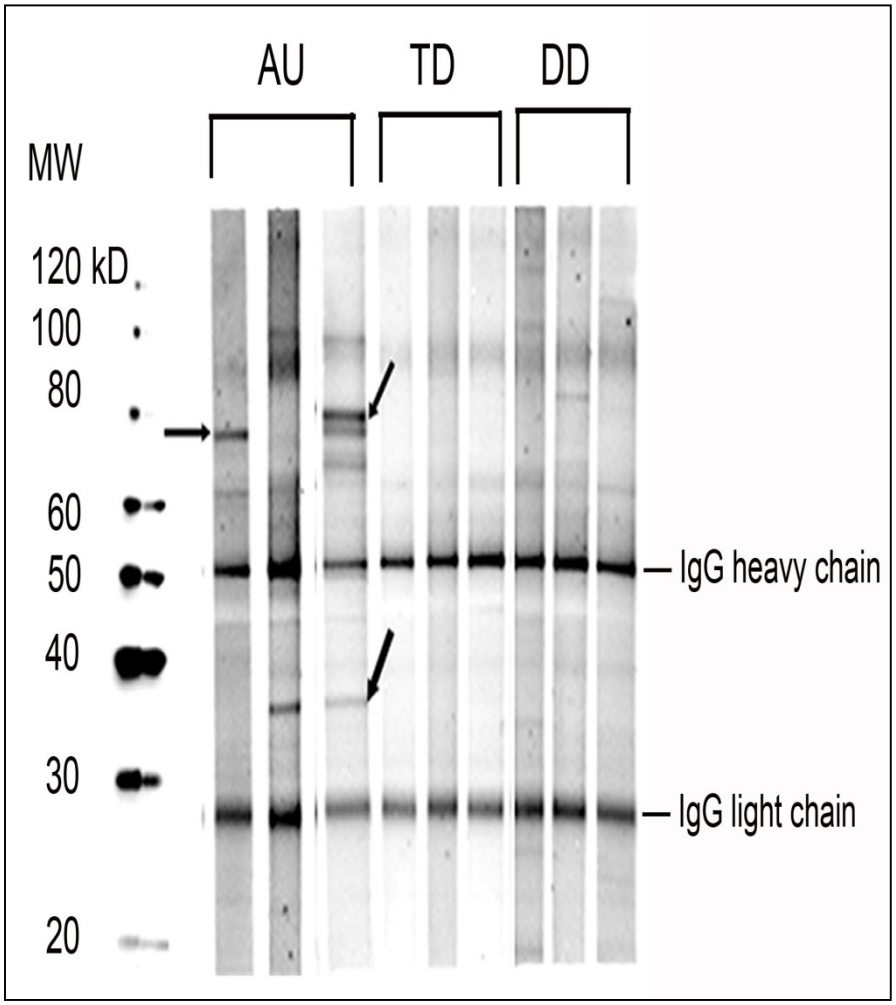
- Maternal history of autoimmune disease

  (Comi 1999, Sweeten 2003)

- Autoantibodies in serum/plasma to fetal brain proteins

  (Braunschweig 2007;Zimmerman2007)

Maternal Autoantibodies to Fetal Brain Postnatal Serum



Postnatal serum from mothers of children with autism (AU), developmental delay (DD) and typical development (TD).

Reactivity of maternal IgG against human fetal brain proteins by western blot.

Braunschweig et al, 2007

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Maternal Immune Function

Prenatal Period

- Infection, asthma, allergy, autoimmune disease during pregnancy
- Altered patterns of inflammatory markers in prenatal serum and amniotic fluid (e.g., cytokines)
- Autoantibodies in prenatal serum to fetal brain antigens

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Maternal
Disorders

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Abstract We
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during pregnan
(ASD). Cases,
ascertained from Kaiser Permanente Norther
clinical databases. No overall association be
noses of any maternal infection during pregnan
was observed [adjusted odds ratio (OR_{adj}) =
confidence interval (CI) 0.92–1.43]. However, women with

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BRAIN, BEHAVIOR, and IMMUNITY

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Prenatal Infection and Autism Spectrum Disorders in Childhood: A Population-Based Case–Control Study in Taiwan

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Abstract

Background: Infection in pregnancy has long been linked with negative postnatal development and health. This study aims to assess the association between prenatal infections and autism spectrum disorders (ASDs) across three trimesters and to probe possible sex heterogeneity in such link.

Method: A total of 4184 children with incident ASDs and 16734 matched children were identified from the 2000–2007 National Health Insurance Research Database. For each child, information pertaining to the mother's infection during pregnancy, sociodemographics, and medical history was retrieved from healthcare records. Conditional logistic analyses were carried out to estimate the strength of associations with adjustment for multiple comparisons.

Result: Pooled analyses demonstrated that having two or more outpatient visits for genital infection [adjusted odds ratio (aOR): 1.34; 95% confidence interval (95% CI) 1.12, 1.60; false discovery rate (FDR) < 0.01] and bacterial infection (aOR: 1.24; 95% CI 1.06, 1.43; FDR < 0.05) in the third trimester were slightly associated with increased risk of ASDs. No statistically significant sex differences were found.

Conclusion: The present study contributes updated population-based evidence about the connection between prenatal infection and ASDs. Potential effect of bacterial and genital tract infections during the third trimester on risk of ASDs warrants further exploration.

Keywords: *autism, children, prenatal infection, sex differences.*

Maternal Infection and ASD

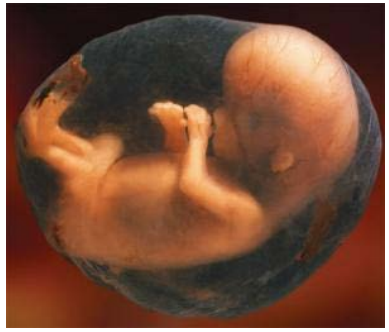
- Several unanswered questions:
  - Which infectious agent? Viral? Bacterial? Parasitic?
  - Timing? 1st, 2nd, 3rd trimester?
  - Infectious agent vs immune response?
    - Fever?
    - increased production of cytokines directly or indirectly impacting the developing fetal brain?
  - Common underlying genetic susceptibility?

Maternal Autoimmune Diseases and ASD

- Similar story:
  - Most studies show an association
  - Specific autoimmune diseases vary
  - Timing during pregnancy varies
  - Autoimmune disease vs immune response?
    - increased production of cytokines directly or indirectly impacting the developing fetal brain?
    - Autoantibodies?
  - Common underlying genetic susceptibility?

Early Markers for Autism Study (EMA)

Investigating early biologic markers of susceptibility and exposure from critical periods of fetal brain development.



Prenatal

Neonatal

Determining etiologic contribution from immunologic and genetic susceptibility factors, environmental exposures, and the interplay of genes with environment

Genetics

Environment

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Early Markers for Autism Study (EMA)

- Population-based case-control study of mother-baby pairs
- California children born 2000 – 2003
  - Phase 1: ~80 ASD, 50 DD, 160 Controls
  - Phase 2: ~ 400 ASD, 400 DD, 400 Controls
- Prospective collection of
  - Maternal second trimester blood
  - Newborn peripheral blood

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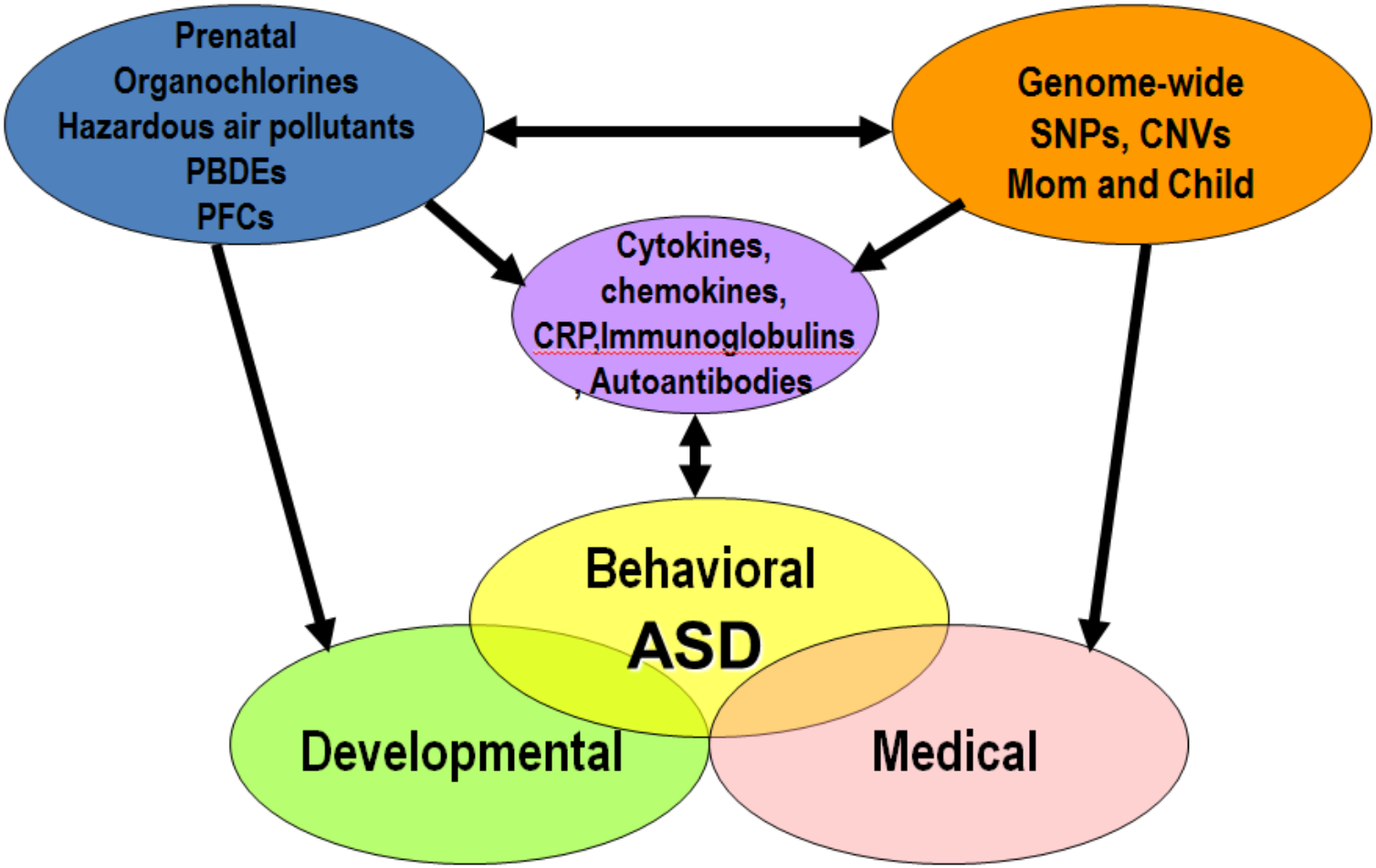
EMA Study



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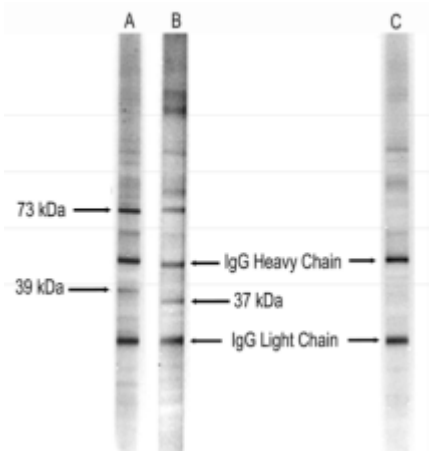
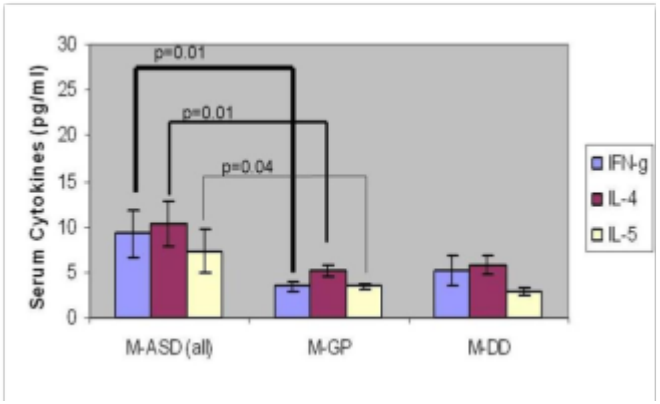
Early Markers of Autism Study (EMA) – Phase 1

Immune system factors associated with ASD risk



Maternal autoantibodies
(Croen et al, 2008)



Maternal cytokines
(Goines et al, 2011)

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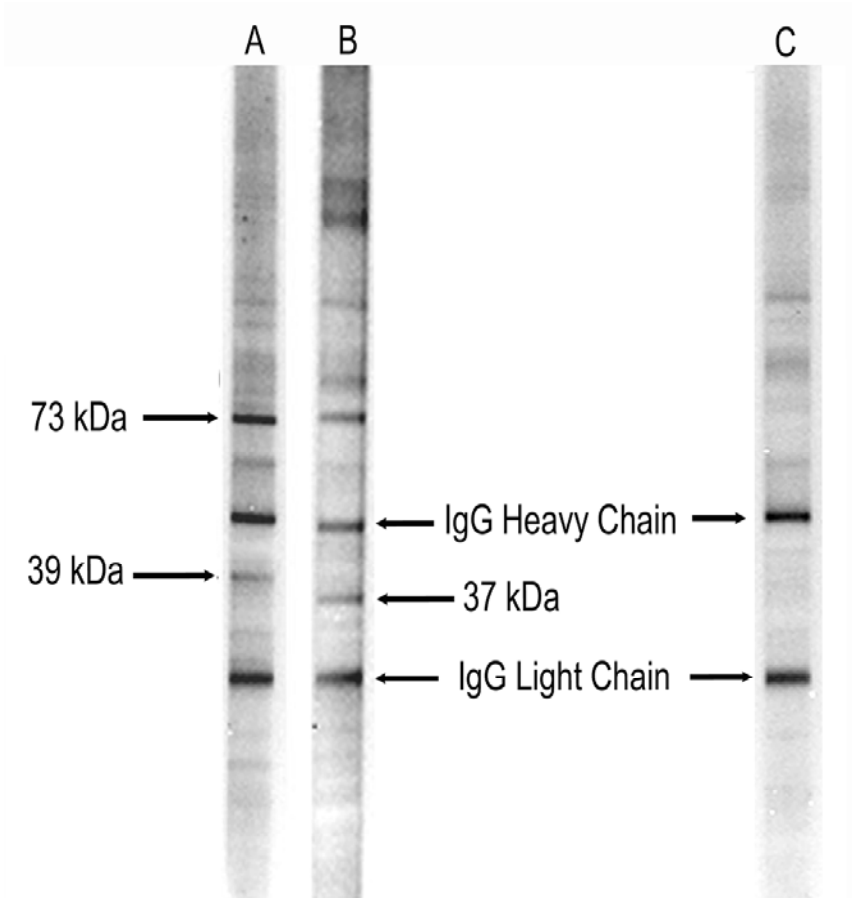
Maternal Autoantibodies to Fetal Brain Prenatal Serum



Lane A: Autism with early onset phenotype with 39kDa: 73 kDa band pattern.

Lane B: Autism with regressive phenotype with 37 kDa: 73 kDa band pattern.

Lane C: Typically developing control child with no reactivity to fetal brain.

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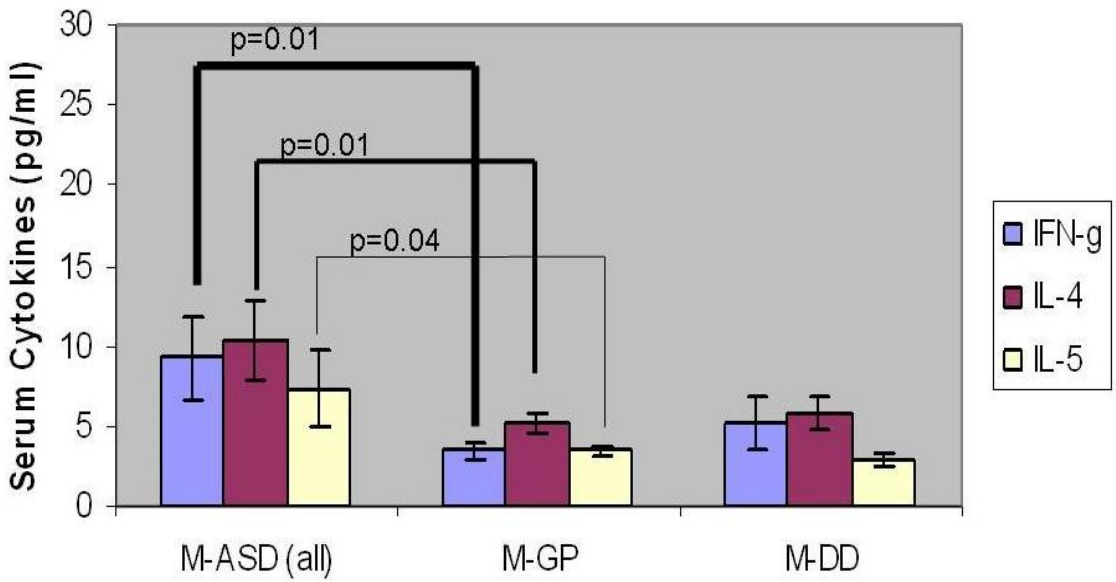
Maternal Prenatal Cytokine Profiles - Phase 1



- IFN- **γ**, **IL**-4, and IL-5 elevated in mothers of children with ASD (M-ASD) compared to mothers of control children (M-GP)
- IFN-**γ**, **IL**-4, and IL-5 levels were highly correlated

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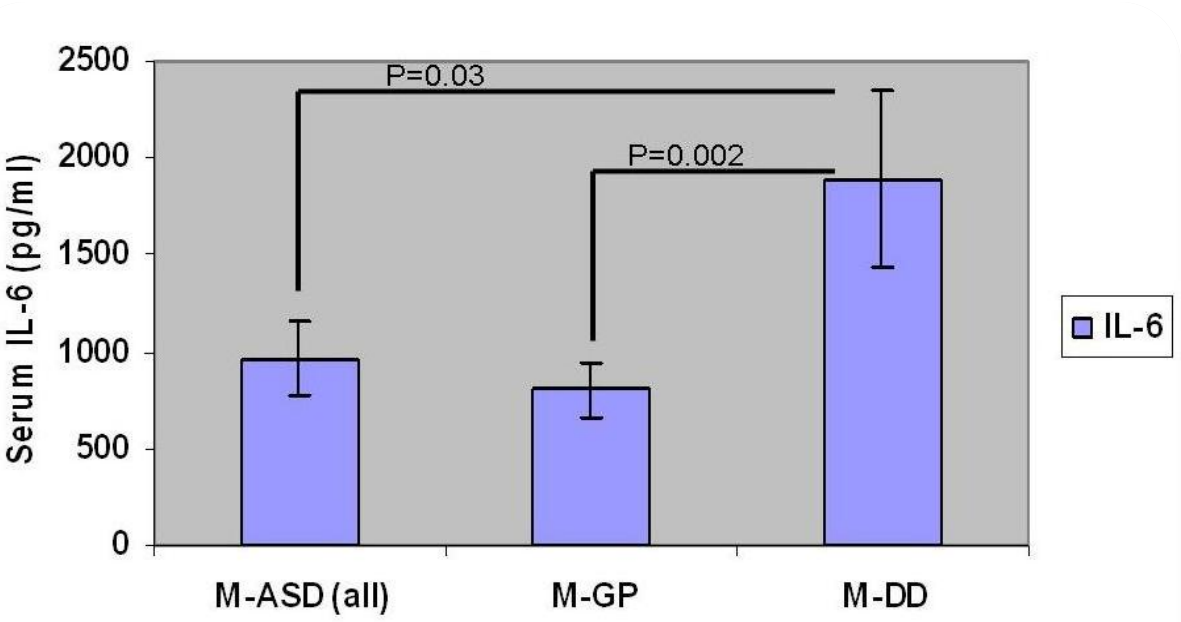
Maternal Prenatal Cytokine Profiles - Phase 1



IL-6 elevated in mothers of children with DD compared to mothers of children with ASD and GP

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Maternal Mid-Gestation Cytokine Elevation: What Does This Mean?

- Increased IFN-γ, IL-4, and IL-5 is consistent with an allergy/asthma phenotype
- Placenta forms a barrier between maternal and fetal circulation, though maternal immune factors including IgG and IL-6 are permitted to cross.
- Even if direct passage is blocked, maternal immune components may react with placental cells that may then alter the fetal compartment.
- This may be the case for IFN-γ, IL-4, and IL-5, which are not known to cross the placenta.

Maternal Prenatal Cytokines - EMA Phase II

		ASD+ID vs. GP	ASD-noID vs. GP	DD vs. GP	ASD+ID vs. DD	ASD-noID vs. DD	ASD+ID vs. ASD-noID
• Growth factor	GM-CSF	0.042	*0.074*	*0.565*	0.041	0.266	0.004
• Innate inflammatory cytokines	TNF-α	*0.055*	0.385	0.375	0.014	0.423	0.022
	IL-1α	0.042	0.277	0.749	0.006	0.589	0.011
	IL-1β	0.093	0.251	*0.055*	0.009	0.919	0.015
	IL-6	0.008	0.468	0.213	0.012	0.675	0.003
• Th1 cytokine	IFN-Y	0.044	0.045	0.870	0.020	0.427	0.003
• Th2 cytokine	IL-4	0.214	0.613	0.956	0.652	*0.083*	0.044
• Regulatory cytokine	IL-10	0.154	0.129	0.226	0.046	0.988	0.022
• Th17 cytokine	IL-17	0.253	0.172	0.492	0.386	0.476	0.035
• Receptor antagonist	IL-1Ra	0.263	0.384	0.177	0.014	0.614	*0.077*
• Innate inflammatory chemokines	IL-8	0.432	0.014	0.003	*0.073*	0.688	0.002
	MCP-1	0.625	0.011	0.032	0.015	0.967	0.001
	MIP-1α	*0.051*	0.107	0.588	*0.086*	0.224	0.003

Mothers of children with ASD+ID had elevated inflammatory T cell and innate immune cell cytokines and chemokines.

These are normally downregulated during mid-gestation.

Suggests a lack of typical immune regulation during pregnancy.

Red = increased risk

Blue = reduced risk

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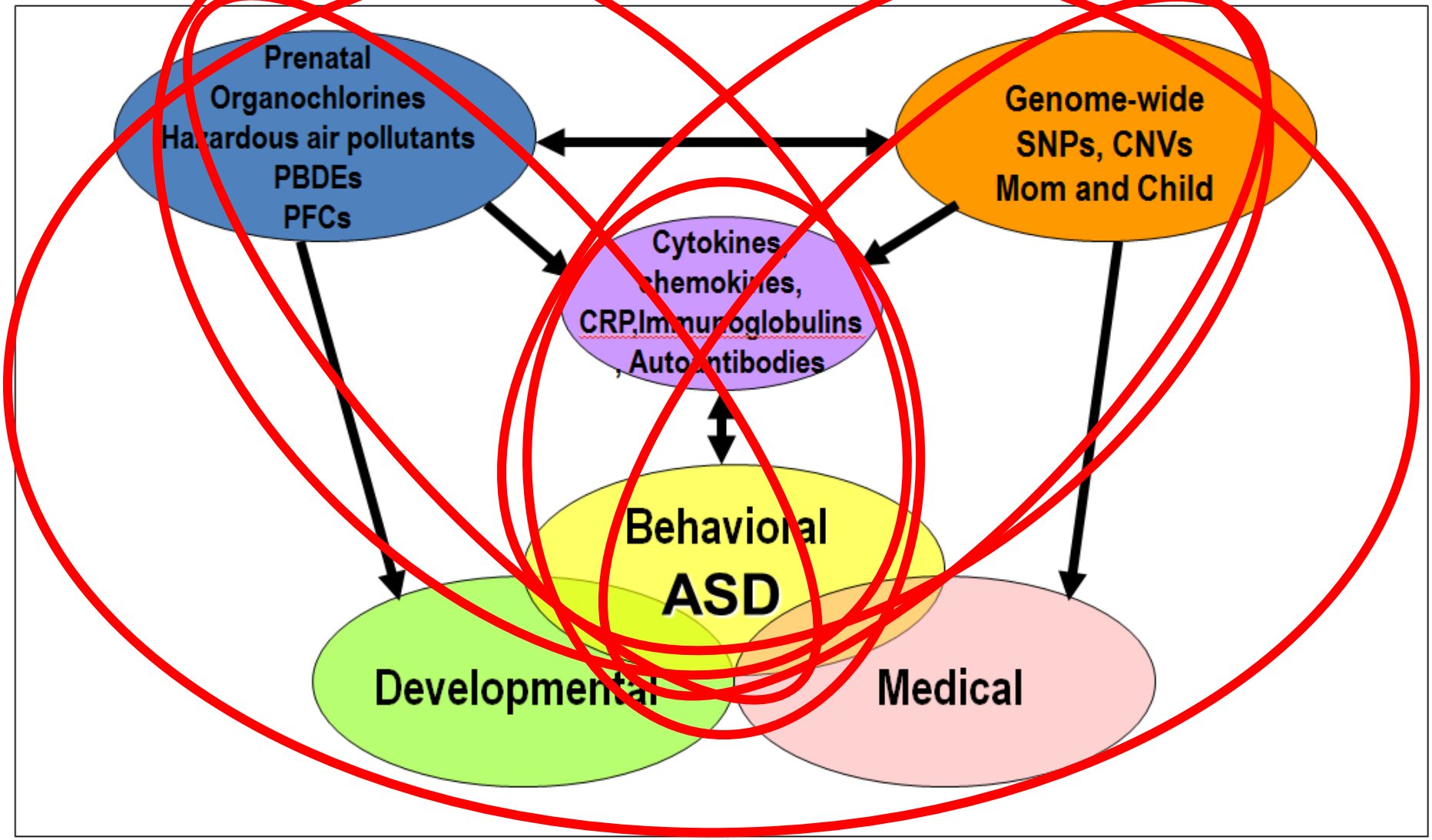
EMA Phase 2 - Ongoing Analyses



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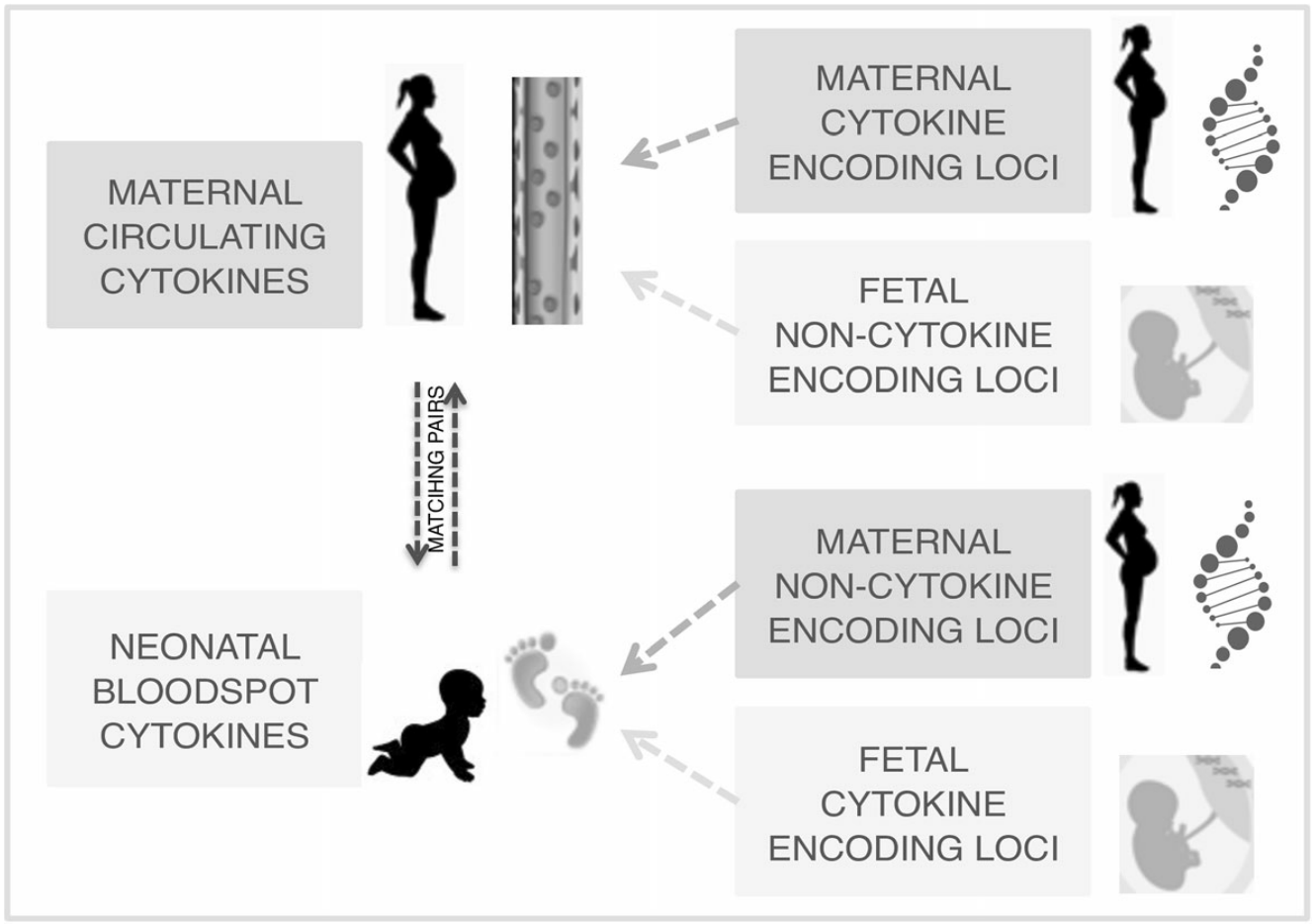

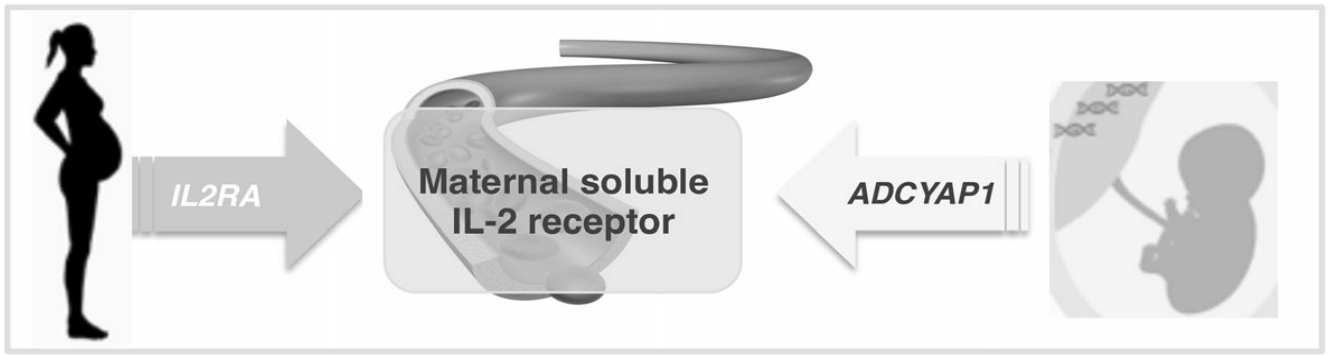

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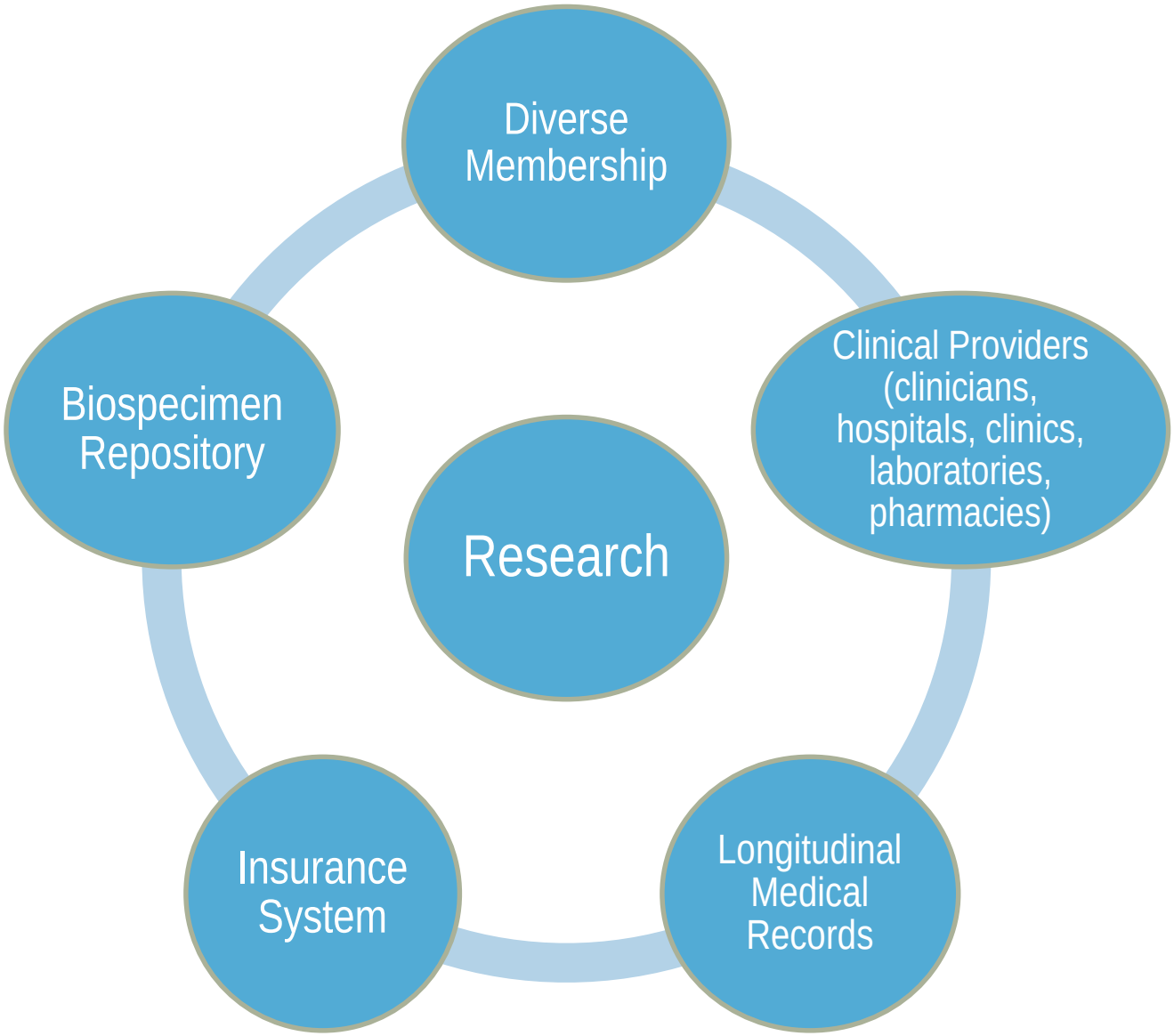
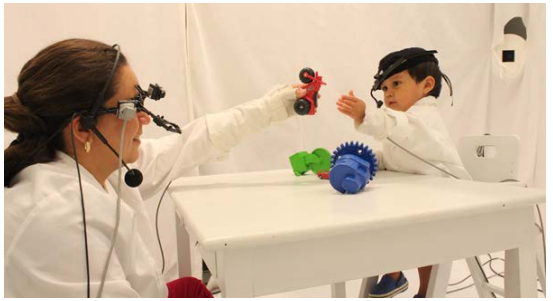
Unique Autism Research Opportunity at KP





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Kaiser Permanente Northern California (KPNC)

- Group practice prepaid integrated health program
- 4.3 million patients
- 9,000 physicians
- 21 hospitals
- Fully electronic health record
- Serves ~30% of population in geographic region

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KPNC ASD Prevalence in June 2018

Age Group	Number of ASD Patients	Prevalence per 1,000
0-4 years	2,827	13.4
5-9 years	5,984	26.2
10-14 years	5,439	22.3
15-17 years	3,046	20.7
18-24 years	5,007	13.9

KPNC Pregnancy Cohort

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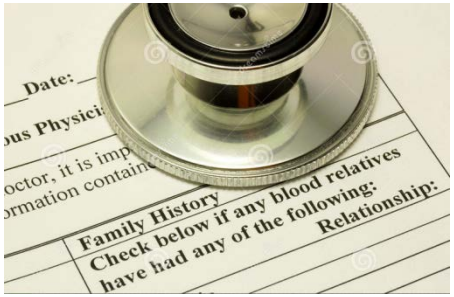

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KPNC Pregnancy Cohort

- ~25,000 enrolled pregnancies
- ~21% overall response rate
- ~78% of participants provided 2 samples
  - 1st trimester samples received at 10 weeks
  - 2nd trimester samples received at 18 weeks
- ~25% completed the survey
- Participants are representative of KPNC prenatal population

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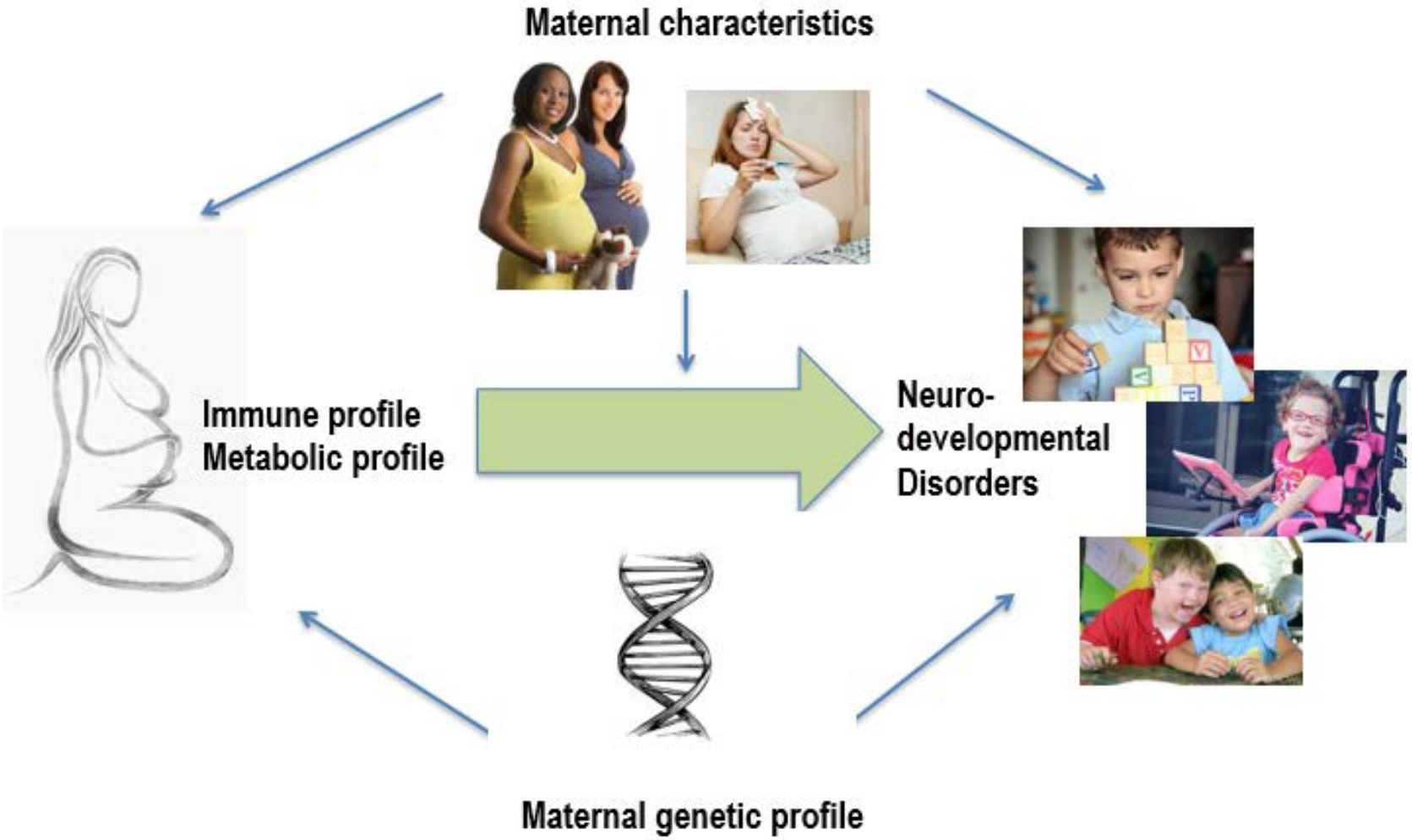
IMPaCT - Immune and Metabolic Markers during Pregnancy and Child Development

Central hypothesis: Maternal inflammation during pregnancy stemming from immune or metabolic dysregulation will adversely impact child neurodevelopment. Further, the timing during pregnancy is important with respect to the specific neurodevelopmental outcome.

Objective: Conduct a longitudinal prospective analysis of maternal gestational inflammatory conditions and their genetic underpinnings in the context of neurodevelopmental outcomes in the child.

IMPaCT Study



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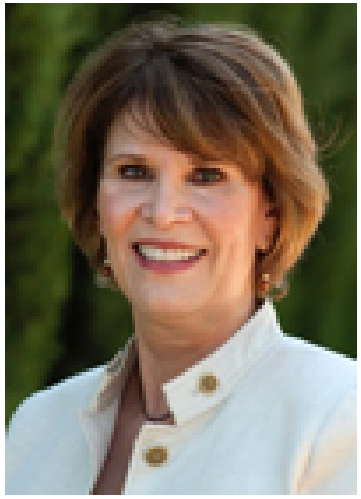
Why is this important?

- We hope to identify patterns of maternal health conditions and biomarkers that indicate risk for specific child neurodevelopmental outcomes.
- Early identification could lead to earlier intervention and the possibility of preventing future morbidity as well as improving quality of life.
- The identification of biomarkers for prenatal risk will shed light on the biologic mechanisms underlying aberrant neurodevelopment, providing an opportunity for developing preventive strategies.

Acknowledgements



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Autism Research Program team at KPNC Division of Research

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