Searching for the Cause of Autism:

How genetics and social experience may intersect

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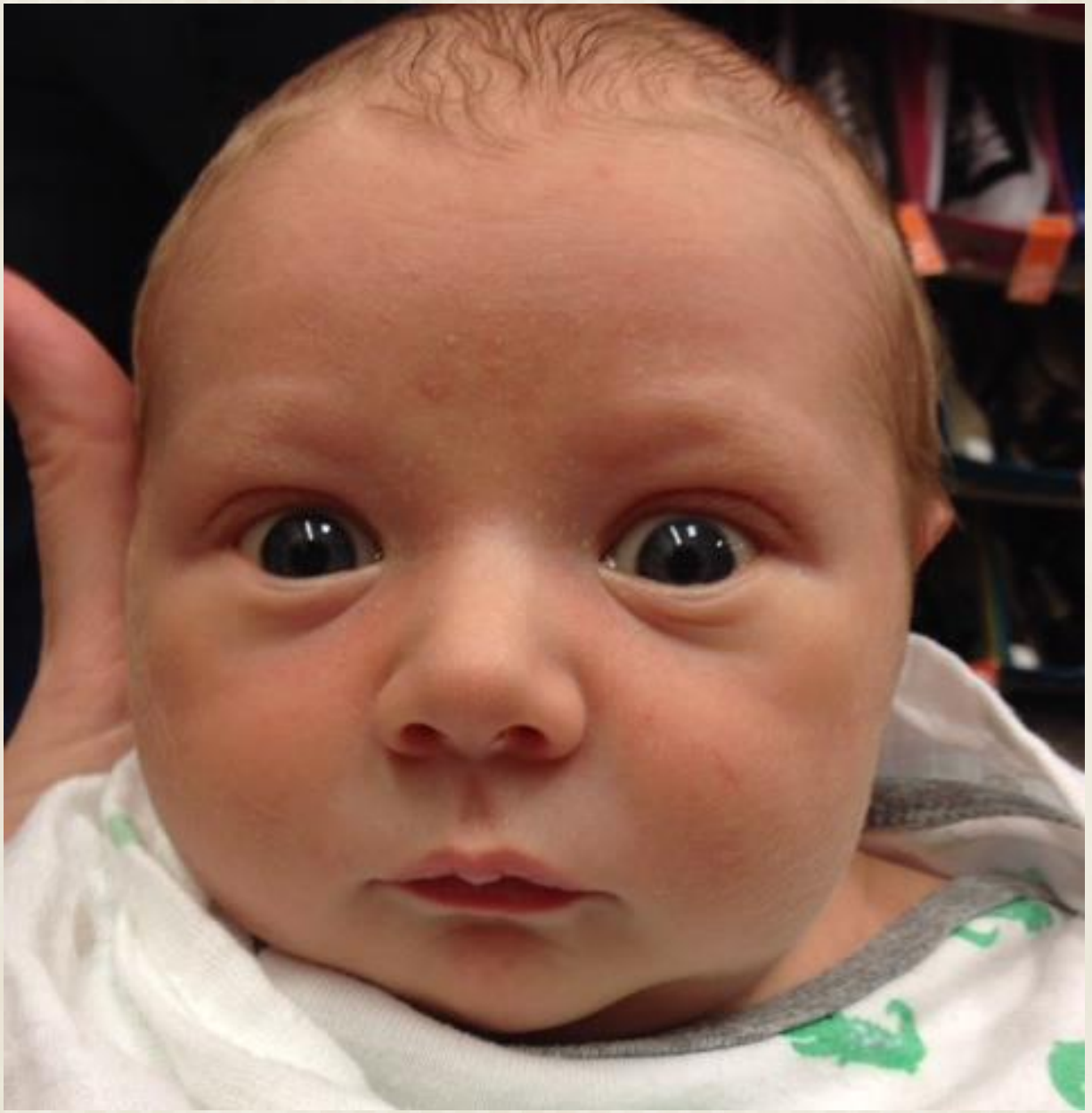

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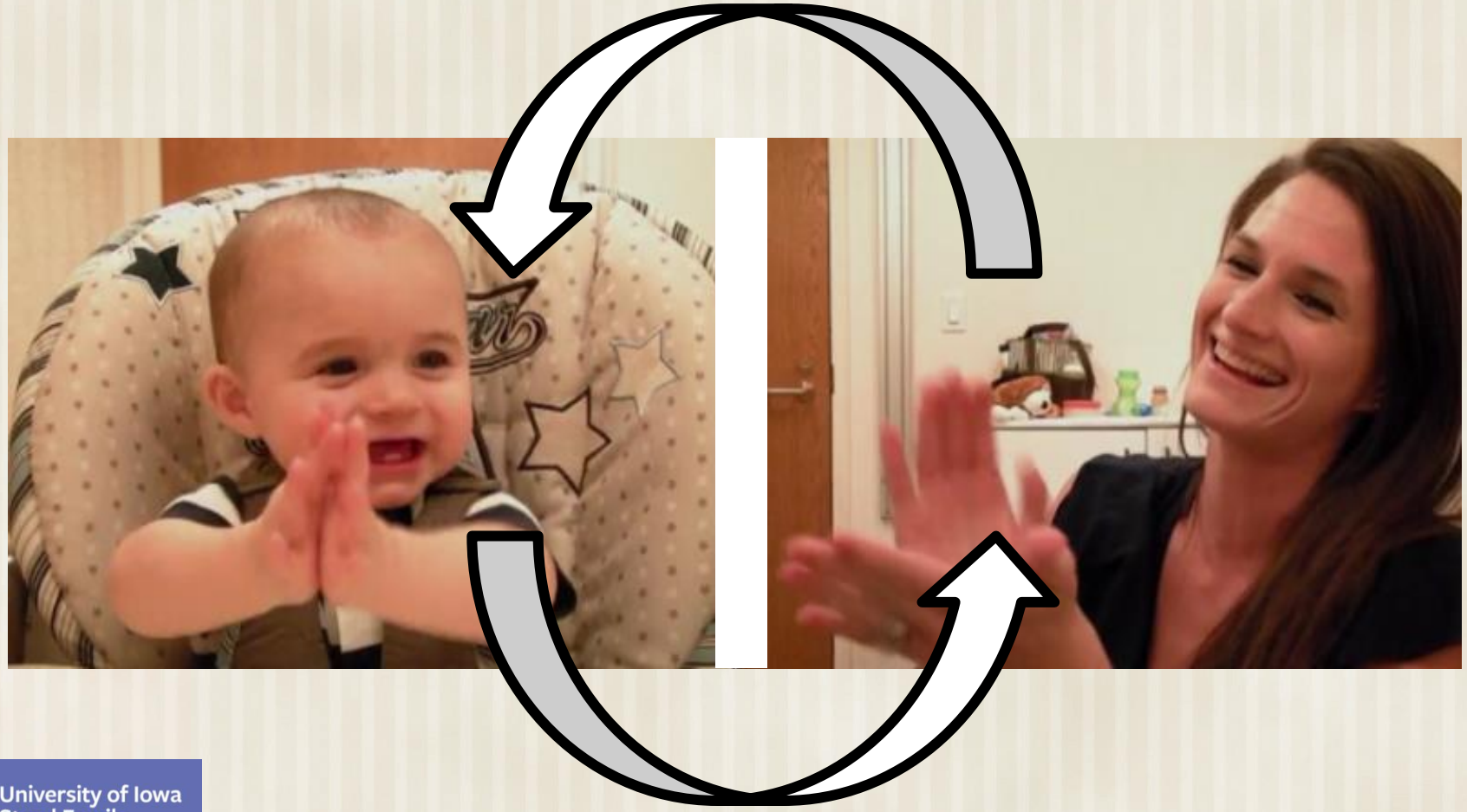


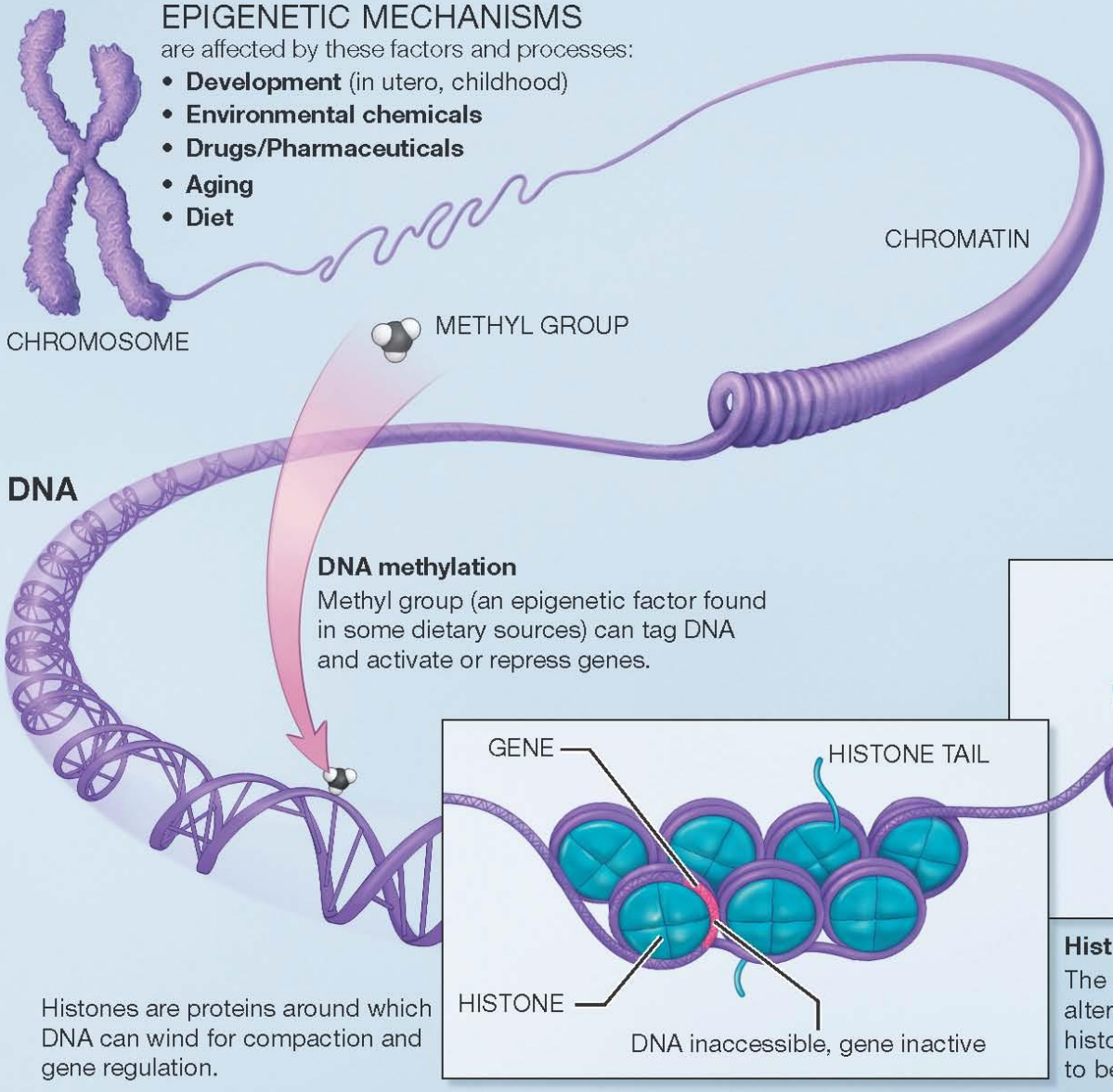
EPIGENETIC MECHANISMS

are affected by these factors and processes:

- **Development** (in utero, childhood)
- **Environmental chemicals**
- **Drugs/Pharmaceuticals**
- **Aging**
- **Diet**

HEALTH ENDPOINTS

- **Cancer**
- **Autoimmune disease**
- **Mental disorders**
- **Diabetes**



DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Epigenetic Regulation of Infant Development

1) Cognitive Development
2) Stress Reactivity
3) Social / Emotional Development

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Phenotype of Autism

1. **Difficulties in Social Communication/ Social Interaction**
   - Difficulty engaging in back-and-forth conversation
   - Difficulties with nonverbal communication
   - Difficulty understanding social relationships

2. **Restricted/Repetitive Behaviors**
   - Repetitive body movements, use of objects, or speech
   - Insistence on sameness
   - Unusually strong interests
   - Unusual interest in sensory aspects of the environment

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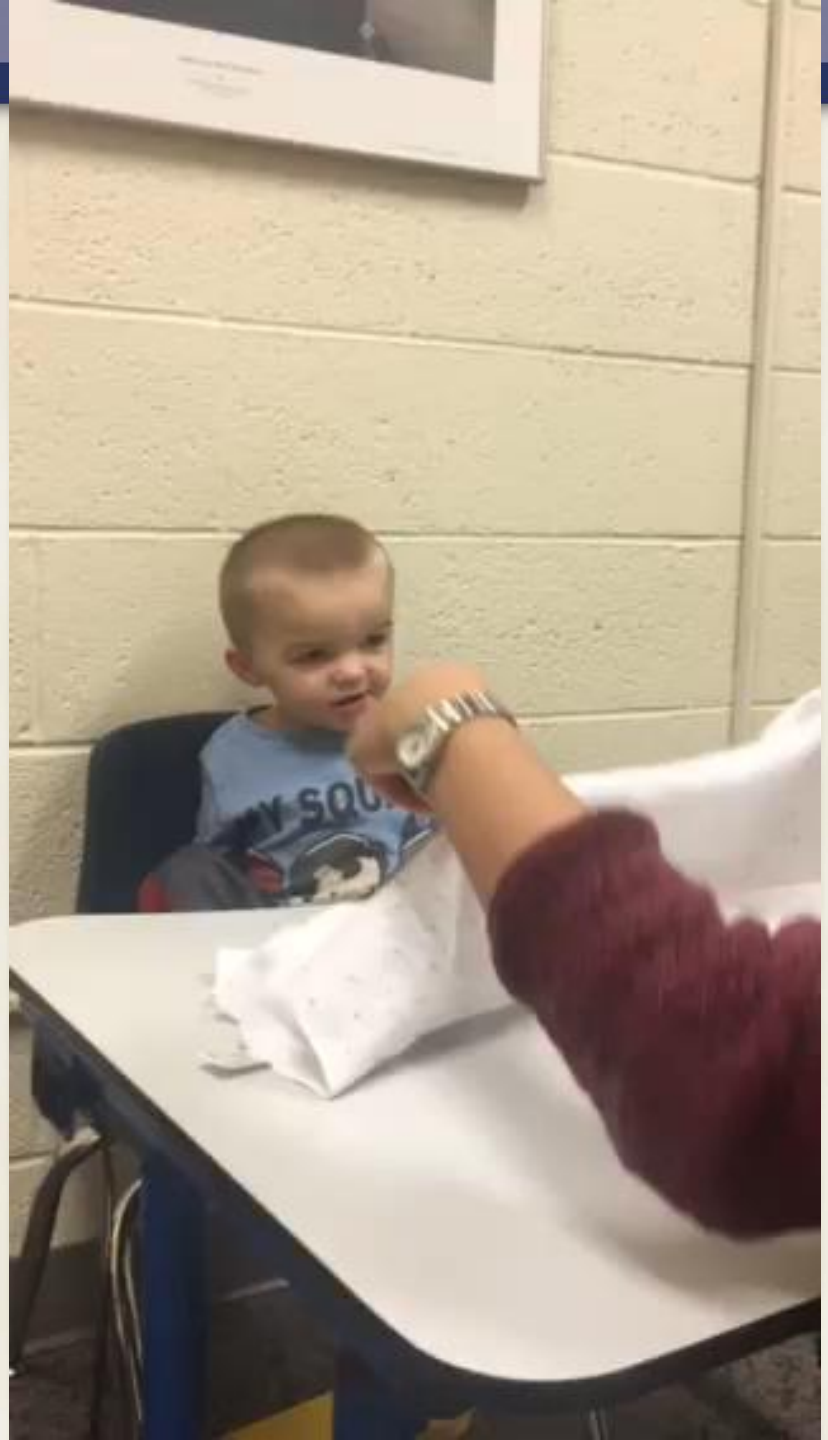

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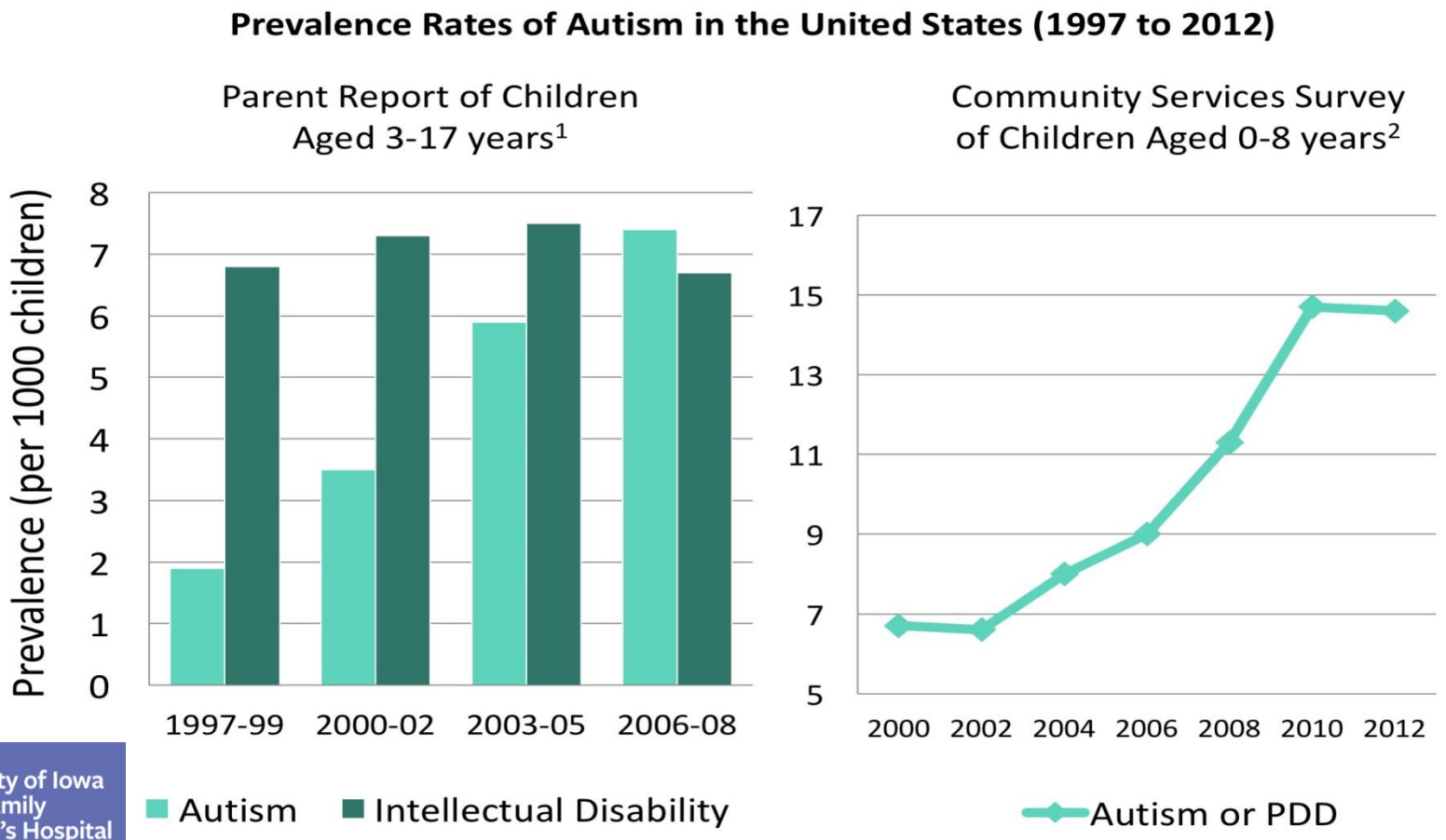
The Problem

- Impact of diagnosis on individual families
- Estimated prevalence has increased:
  - 2-5 in 10,000 (in 1977) to 1 in 45 today in US (Xu, Strathearn, Bao, 2018)
- Possible reasons:
  - Broadened diagnostic criteria
  - Inclusion of cases with known genetic causes or severe mental retardation
  - True increase in prevalence?
- Implications for public health:
  - Escalating demand for education and therapeutic resources, with intensive therapy currently the only recognized intervention

The Problem



[1]*Pediatrics.* 2011;127(6):1034-42. [2]*MMWR Surveillance Summary*. 2016;65(3):1-23.
PDD, Pervasive developmental disorder.

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Proposed Etiologies

1940s	• "Infantile autism" first described by Kanner (1943) and later, by Hans Asperger • Initially thought to be of neuropathological origin
1950s	• Described as "Refrigerator Mother" Syndrome, implicating parenting deficiencies
1970s	• Twin studies suggest genetic etiology
1990s	• Widespread public concern about "environmental etiology" e.g. MMR vaccination
2000s	• Proposed genetic predisposition with "second hit" from environmental factors

Associated Family Characteristics

Parent of autistic children more likely to display:

- Social reticence
- Communication difficulties
- Preference for routines and difficulty with change
- Recurrent depression and anxiety disorders
- Increased head circumference

Etiology of Autism

Genetic Etiology

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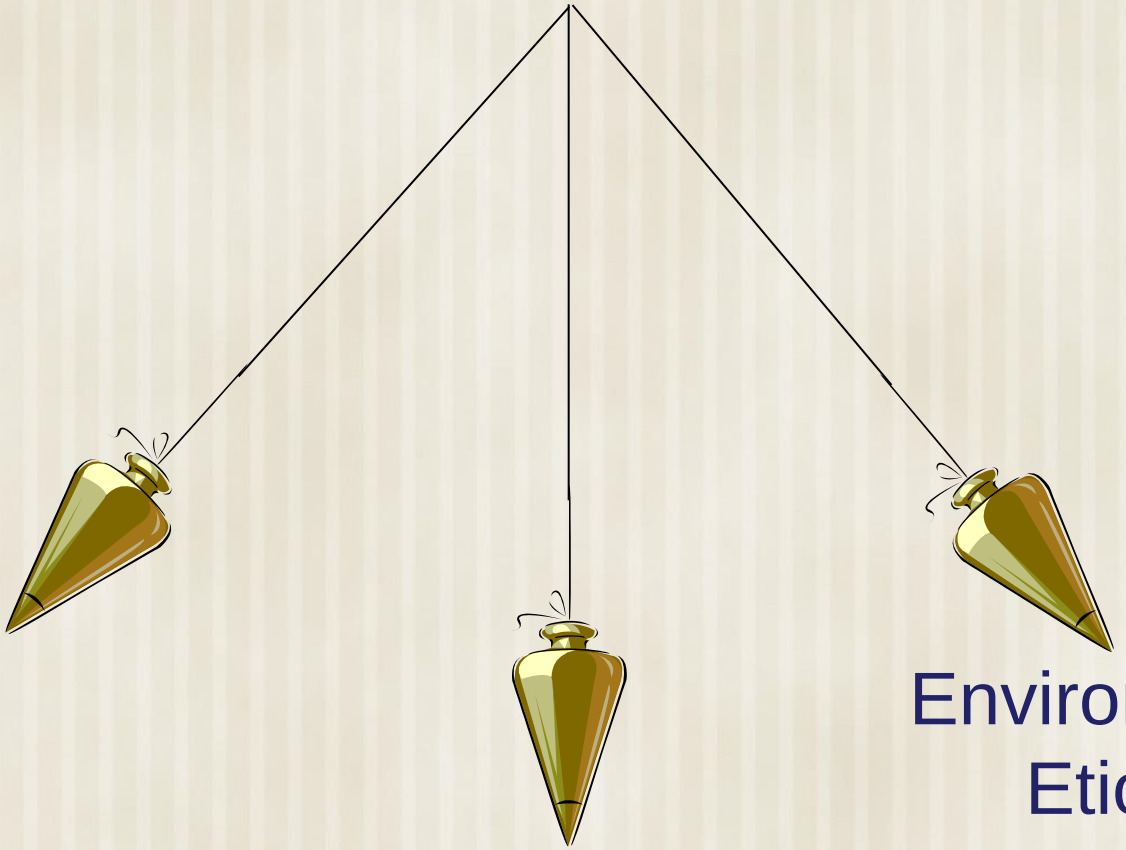
Etiology of Autism

Environmental Etiology

Etiology of Autism



Genetic Etiology

Environmental Etiology

Genetic Predisposition + Environmental "2nd Hit"

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Evidence for Genetic Etiology

- Increased incidence in siblings
  - Almost 100-fold increase in relative risk compared with general population
- Higher concordance rate in monozygotic twins
  - 36-91% compared with <1% in dizygotic twins
- Association with several specific genetic disorders, e.g.
  - Fragile X disorder, Angelman Syndrome
  - Rett Syndrome

Evidence for Genetic Etiology (cont.)

- Genetic susceptibility markers identified on genome-wide array analyses
  - Genes encoding for neuronal cell adhesion molecules (Wang, 2009)
  - Copy number variations (Glessner, 2009)
  - Genes regulated by neuronal activity (Morrow, 2008)
- However, individual markers explain only small amount of variance
- Epigenetic factors

DNA Methylation and Epigenetics

- Early life somatosensory stimulation results in hypomethylation of stress gene promoter, resulting in enhanced hippocampal stress hormone receptor expression and a reduced HPA stress response
- Could early life experience play an epigenetic role in the development of neurodevelopmental disorders, such as autism?

Evidence for Social/ Environmental Factors in Autism

- A high proportion of Romanian adoptees with severe early privation found to display autistic features (6% + 6% with milder autistic features)
  - Symptoms related to severity of deprivation
  - Indistinguishable from other autistic patients on ADI/ADOS
  - Differences includes equal sex ratio, normal head circumference, and some improvement by age 6
- Higher rates of autism also seen in congenitally blind children

Evidence for Social/ Environmental Factors in Autism

- Abundance of literature supporting the role of maternal behavior in programming infant neural development
  1. **Cognitive development** (hippocampal L-LTP, synaptogenesis, spatial learning and memory)
  2. **Stress reactivity** (CRF production, GR and Carbamazapine A receptor expression, behavioral manifestations of anxiety)
  3. **Social behavior** in female offspring (Oxytocin and estrogen receptor expression, licking/ grooming/ nursing behaviors)

Oxytocin

- 9 amino acid peptide synthesized in the hypothalamus and released into the bloodstream via the post pituitary
  - Uterine contraction in childbirth
  - Milk let down during suckling
- Central neuromodulatory effects also present
  - Maternal care
  - Female pair bonding (voles)
  - Decreases infant isolation distress call
  - Improved social memory and spatial learning/memory (e.g. mouse knockout models) (Ferguson et al, 2000)
  - Pup grooming/stereotypies (Pederson, 2002)
- Released in CNS in response to non-noxious sensory stimulation (light touch, warmth, etc)

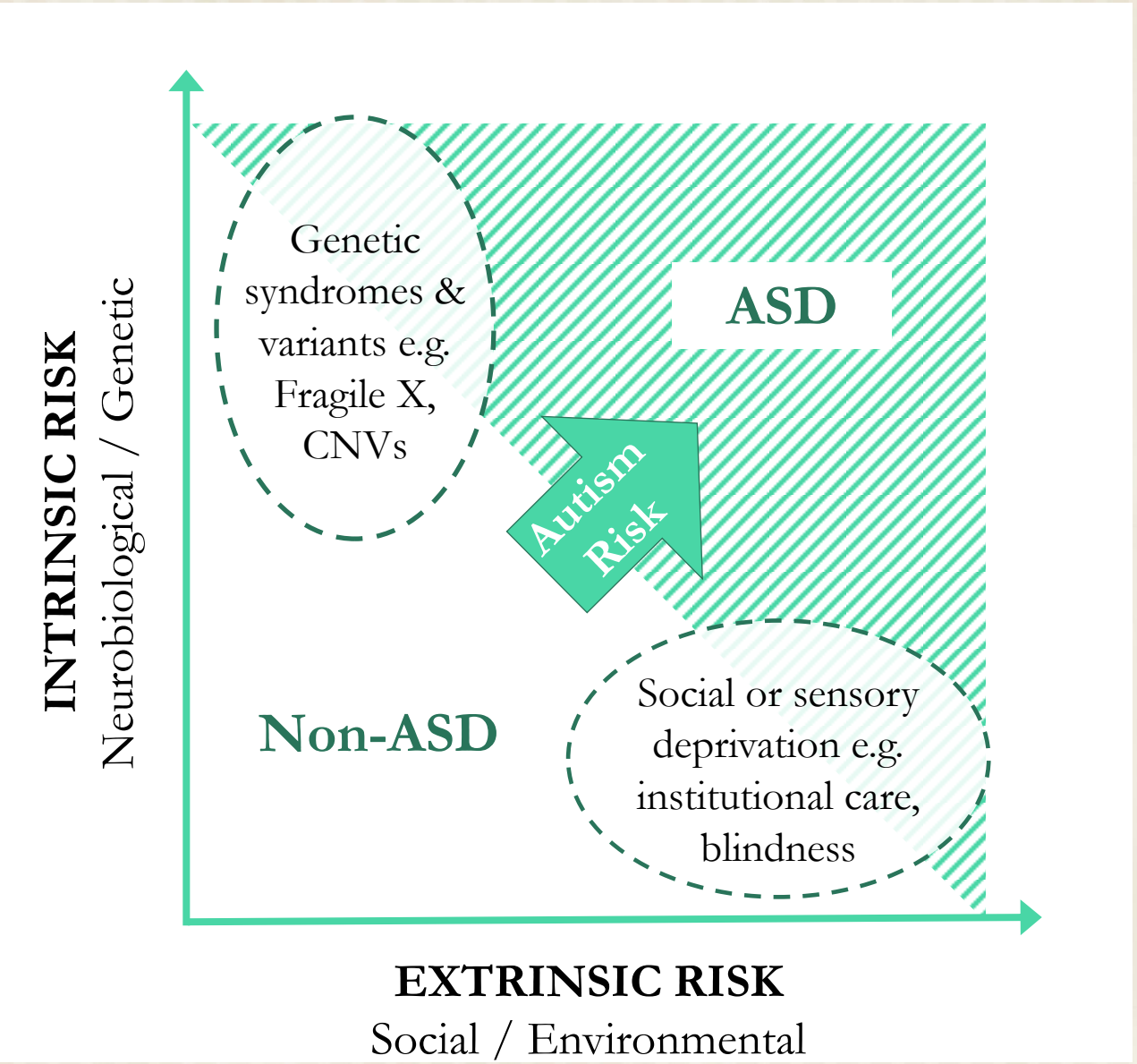
Oxytocin (OT) and Autism

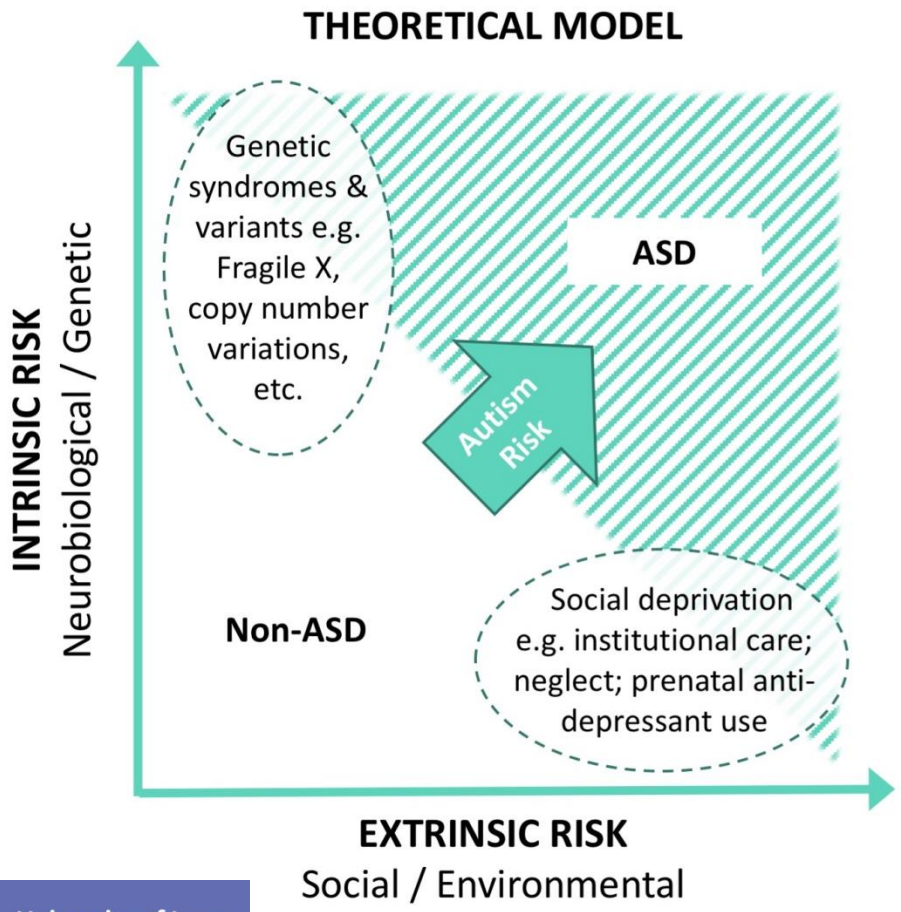
- Adults with autism have lower plasma OT concentrations than controls (Modahl, 1998; Green, 2001)
- Intravenous OT infusion reduces stereotypic behaviors in adults with autism (Hollander, 2003)
- Intranasal OT results in enhanced emotion recognition (Guastella, 2010) and social behavior (Andari, 2010).

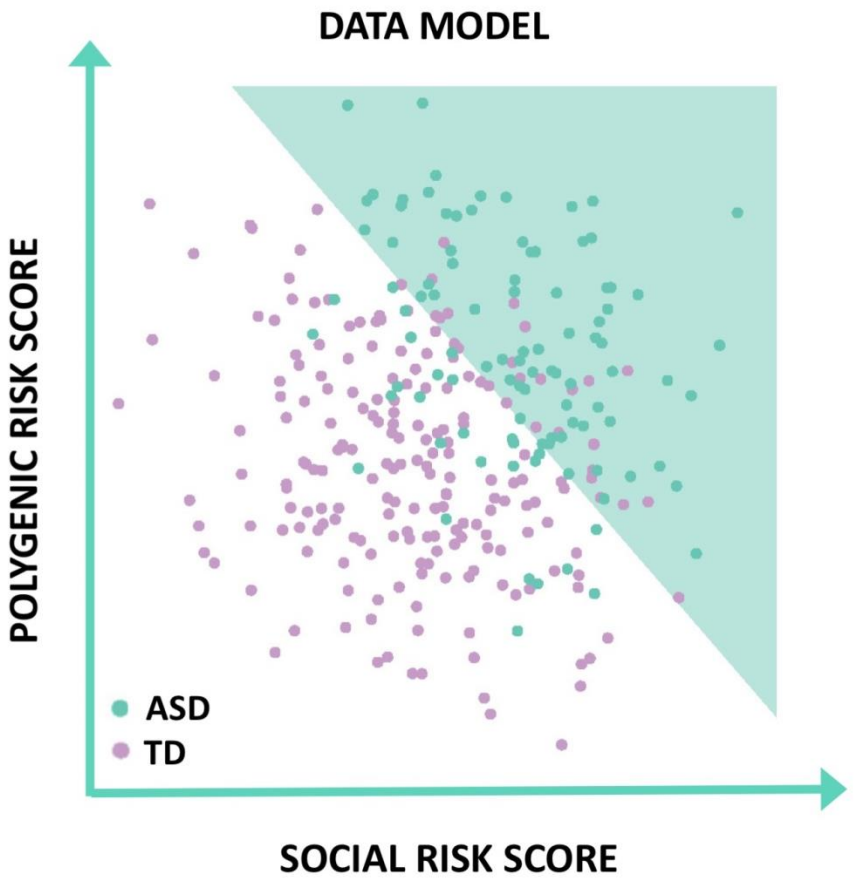
Face Processing and Autism

- Key role of social perception in the development of autism
- Face processing impaired in children with autism (ERP and fMRI studies)
- Development of face perception occurs during infancy and early childhood
- Eye gaze aversion, a core characteristic of autism, is not present from birth, but develops over the first 6 postnatal months (Jones and Klin 2013).

Theoretical Model of Autism Risk







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Study Design

- Enroll pregnant women and download smart phone app
- Collect data during pregnancy
  - Experience of stress, depression, social support, pregnancy complications
- Video record infant/child social development using smart phone over first 2 postnatal years
- Test for polygenic risk for autism from newborn blood samples
- Screen for autism or other developmental delays at 2 years

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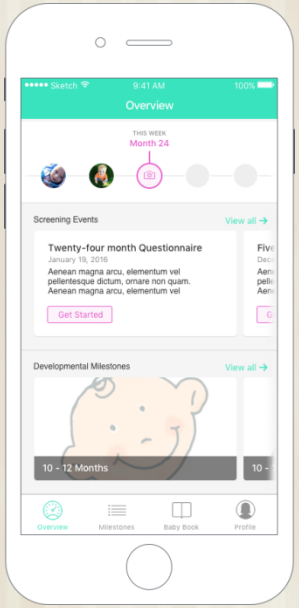

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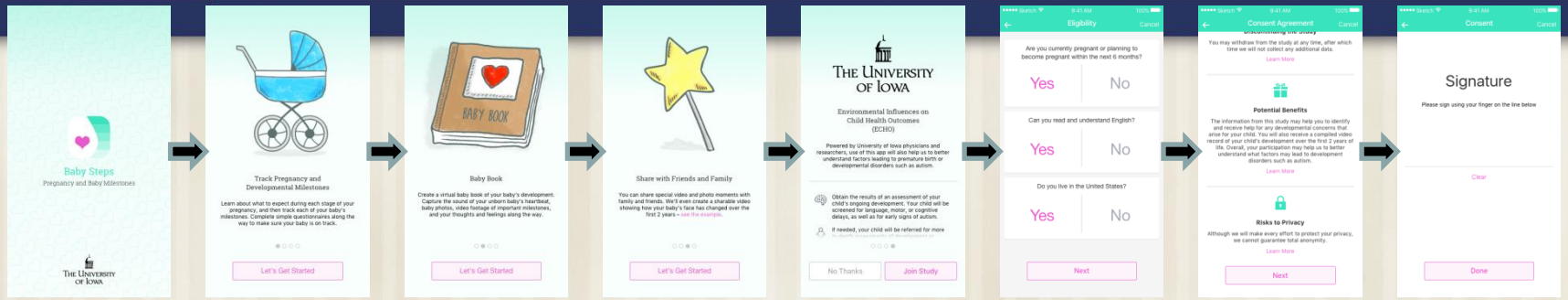
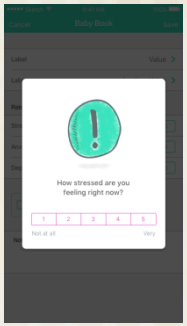
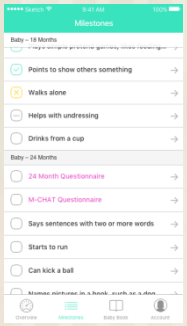
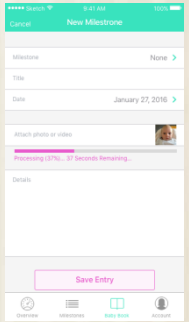


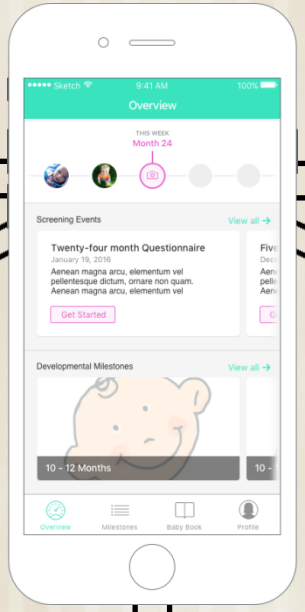


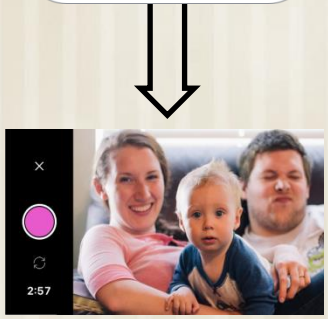
ECOLOGICAL MOMENTARY ASSESSMENTS (EMA)



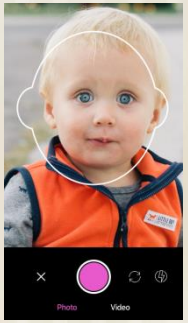
DEVELOPMENTAL MILESTONE SCREENING AND CAPTURE



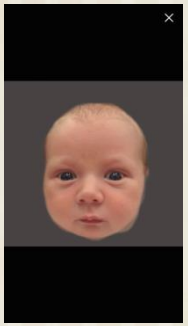




VIDEOTAPED SOCIAL BEHAVIOR



VIRTUAL BABY BOOK PHOTOS AND VIDEOS



BABY FACE MORPH VIDEO


9:41 AM
100%
Baby Steps
Phone
Mail
Messages
Safari

Future Plans

- Complete smart phone app development
- Marketing campaign throughout Iowa to enroll pregnant women in study
  - Work with local obstetricians and practitioners
  - Advertisements
  - Social media presence
- Expand to other states and overseas
  - Collaborators in Shenzen, China

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