

Baylor  
College of  
Medicine



**Texas Children's  
Hospital®**

# *Developmental Regression in Autism Spectrum Disorder: What Do We Know and Where Do We Go?*

Robin P. Kochel, Ph.D.

Associate Professor, Pediatrics, Baylor College of Medicine

Director of Research, Autism Program, Texas Children's Hospital

Baylor College of Medicine

# Overview

- Definition of regression
- Brief history of research on regression
- Prospective approach to identifying regression
- Factors associated with regression
- Value of studying regression
- What to do if you suspect regression

*"I've now gone to thinking that almost all kids with ASD experience regression."*

*"I think regression is on it's way out."*



# Defining Regression in ASD

- *The act of going back to a previous place or state* (dictionary.com)
- *Loss of previously acquired skills*
- Kanner (1943) noted parent report of regression in one of his original 11 cases:

*“I can’t be sure just when he stopped the imitation of words or sounds.  
It seems that he has gone backward mentally, gradually for the last two years.”*

~Mother of Richard, age 3 years 3 months

# Characterizing Regression in ASD Onset: 1956—2000

- Language loss with poor prognosis (Eisenberg, 1956)
- Three ASD trajectories, including loss of speech (Creak, 1961)
- First epidemiological study of autism noted 31.3% with a loss of some ability (Lotter, 1966)
- Clear loss of previously acquired language skills accompanied by stagnant development and emergence of other ASD symptoms (DeMyer, 1979; Kurita, 1985; Rogers & DiLalla, 1990)
- Questioning the existence of regression (Volkmar et al., 1985)
- Emerging reports but inconsistent in characterization—> validity in question

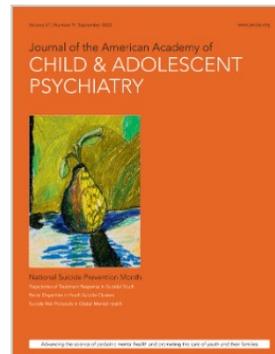
# Studying Regression: 2000—2010

- Various groups examined prevalence and timing of regression in the early 2000's
- Prevalence = **one-third of children with ASD** (Baird et al., 2008; Goldberg et al., 2003; Luyster et al., 2005; Werner et al., 2005)
- **Average age at loss = 21.4 months** (Barger, Campbell, & McDonough, 2013)
- Different methodologies afforded validation of regression as a true event
  1. Video study (Goldberg et al., 2008; Maestro et al., 2006; Werner & Dawson, 2005)
  2. Clinician-rated prospective study (Ozonoff et al., 2010)



# Prospective Study of ASD Onset (2010)

- Prospective, longitudinal comparison of 25 infants later diagnosed with autism and matched controls without ASD
- Clinician ratings of social-communication behaviors in per-minute segments at 6-month intervals from 6—36 months
- **86.4%** of infants later diagnosed with ASD demonstrated **significantly declining trajectories**
- Differences between groups were on a very small scale for most behaviors and at most ages (e.g., 3 gazes per minute vs. 2)



## A Prospective Study of the Emergence of Early Behavioral Signs of Autism

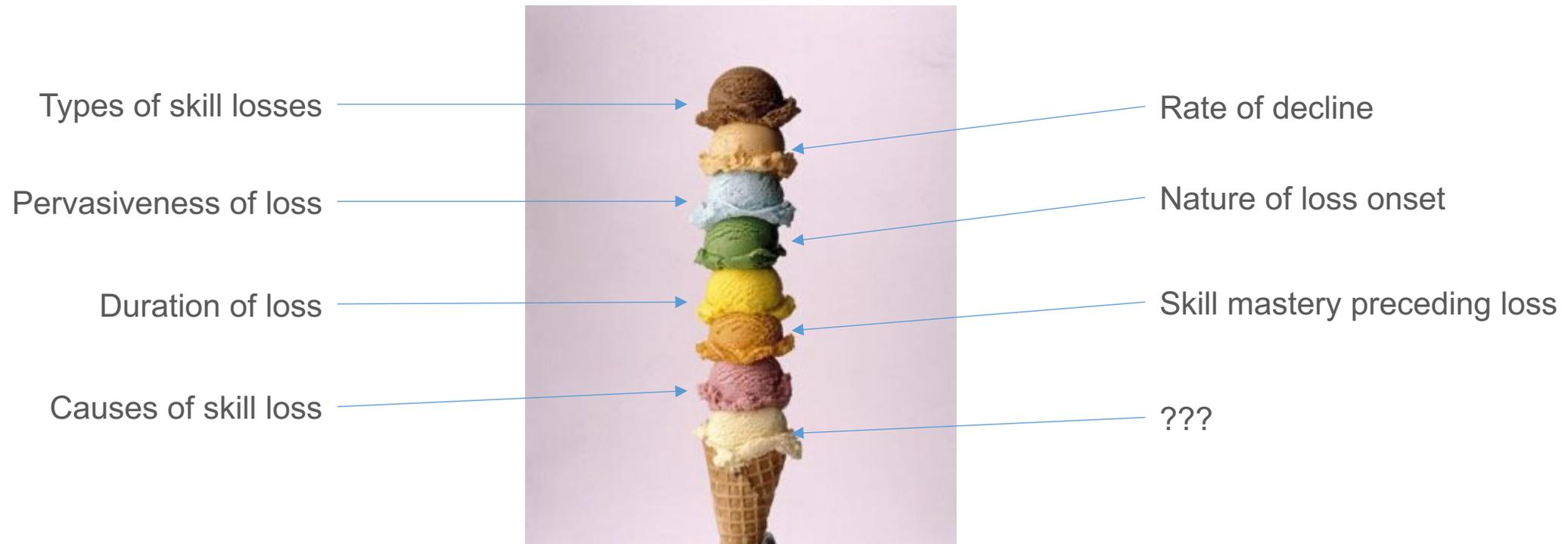
Sally Ozonoff, Ph.D., Ana-Maria Iosif, Ph.D., Fam Baguio, B.S., Ian C. Cook, Ph.D., Monique Moore Hill, M.S., Ted Hutman, Ph.D., Sally J. Rogers, Ph.D., Agata Rozga, Ph.D., Sarabjit Sangha, B.S., Marian Sigman, Ph.D., Mary Beth Steinfeld, M.D., Gregory S. Young, Ph.D.

# Implications

- Concluded that most children with ASD regress as the onset of symptoms
- Is this still regression?
  - Skill *decline* vs. skill *loss*
- Highlighted the variance in results with different methodologies
- Lower rates of skill loss are reported in surveys and interviews
- Retrospective approaches may miss important losses and result in inaccurate groupings of children
- Prospective, clinician-rated methods are costly, time-consuming, impractical for future study and implementation in clinical practice
- Alternate approaches need to be considered

# Conceptualizing Regression in ASD

- Varied/expanded definitions and continued study of regression over time reflect a complex phenomenon



# “Flavors” of Regression in ASD



# Studying Regression: 2010—present (2021)

- Meta-analysis of 75 studies on regression (33,014 participants)
- **30% (CI: 27% - 32%) with regression**
- **Average age at loss = 19.8 months**
- Need for a common definition and standardized tools to measure skill loss at different points in time



## Prevalence and Age of Onset of Regression in Children with Autism Spectrum Disorder: A Systematic Review and Meta-analytical Update

Christine Tan, Veronica Frewer, Georgina Cox, Katrina Williams, Alexandra Ure 

# INSAR: Regression Special Interest Group (SIG)



- International team leading a SIG on Regression or Skill loss in Autism
  - Lead: Katrina Williams, Co-Lead: Chirag Mehra
- 3-year initiative
- Maximize collaborative research activities and data sharing through the following actions:
  - Providing an overview of what is known about regression and identify gaps
  - Developing an operational definition of regression
  - Developing approaches to achieve agreed minimum standards for datasets and data sharing
  - Developing approaches to progress toward assessments that evaluate key retrospective/historical and phenotypic/clinical presentations
  - Developing approaches to progress toward outcome measurement agreement
  - Developing best-care clinical assessment of cause
- *Looking for self advocates and family members who experienced or witnessed regression to join our SIG!*

Why is it valuable to study regression in ASD?

# 1. Regression May Affect Medical and Functional Outcomes

- Compared to children with ASD without regression, children who regress are more likely to have
  - Co-occurring **psychiatric diagnoses** (Matson, Wilkins, & Fodstad, 2010)
  - **Sleep problems** (e.g., delayed sleep onset, nighttime awakenings) (Giannotti et al., 2008)
  - **Seizures** (Zhang et al., 2012)
- Differences between children with/without regression
  - Cognitive functioning/IQ
  - Adaptive functioning
  - ASD symptom severity

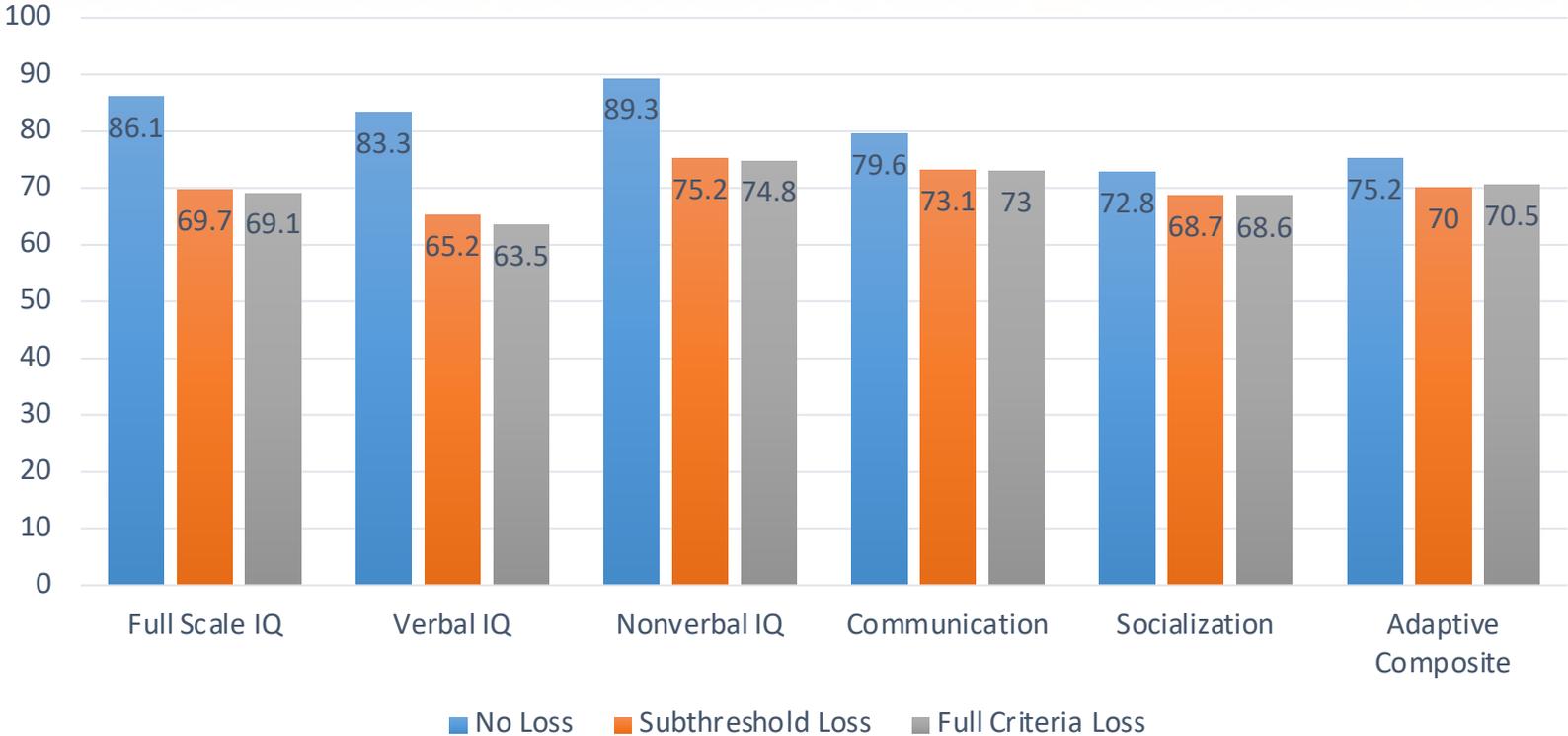


# Associations with Cognitive & Adaptive Functioning

- Mixed findings
- No differences between groups (Lord, Schulman, & DiLavore, 2004; Shumway et al., 2011)
- Group differences (Bernabei et al., 2007; Wiggins, Rice & Baio, 2009)
- Mixed results related to *degree* of loss (Kalb et al., 2010; Parr et al., 2011)
- Differences on some measures but not others (Werner et al., 2005; Richler et al., 2006; Baird et al., 2008)

# Regression and Cognitive & Adaptive Functioning (2014)

## Differences in Cognitive and Adaptive-functioning Scores in 2105 SSC Participants: Language Loss

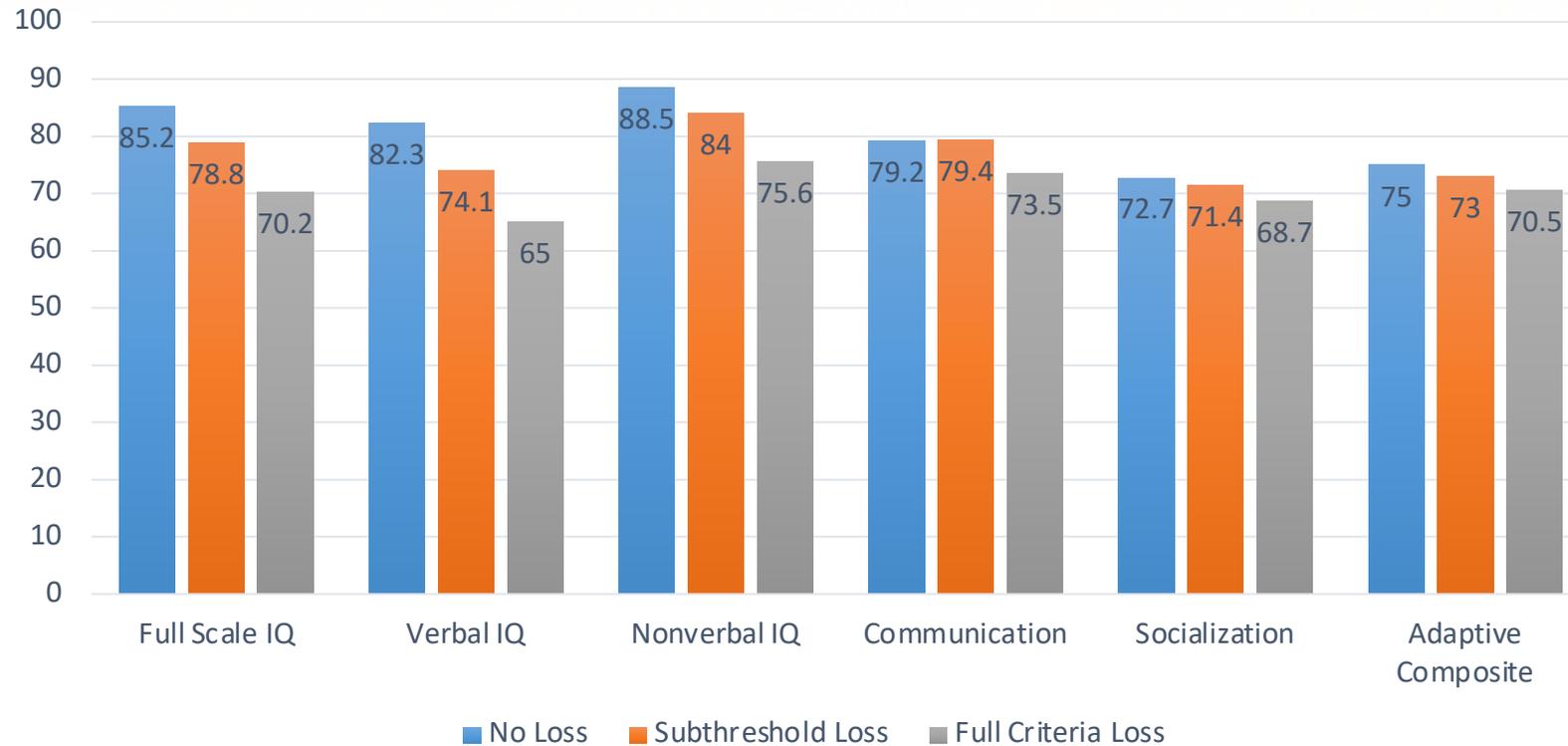


Developmental regression among children with autism spectrum disorder: Onset, duration, and effects on functional outcomes

Robin P. Goin-Kochel<sup>a,\*</sup>, Amy N. Esler<sup>b</sup>, Stephen M. Kanne<sup>a,1</sup>, Vanessa Hus<sup>c</sup>

# Regression and Cognitive & Adaptive Functioning (2014)

## Differences in Cognitive and Adaptive-functioning Scores in 2105 SSC Participants: Other Loss



# Regression at Time of Diagnosis (2022)

- Chart review of 500 toddlers with ASD diagnoses (18-36 months)
  - Diagnoses at 24.7 months in children with regression, 26 months for those without
- Regression defined as:
  - Clinician documented “regression” in the chart
  - Either referral to subspecialist OR metabolic laboratory studies ordered
- **4%** (20/500) met criteria for regression
- Those with regression had lower developmental, language, and adaptive functioning scores, but no differences in motor scores or ASD symptoms

## Description of Clinician-Diagnosed Regression at Time of Autism Spectrum Disorder Diagnosis in Toddlers

Zaro, Christopher BS\*;  Harris, Holly MD†; Sideridis, Georgios PhD\*; Barbaresi, William MD\*;   
Harstad, Elizabeth MD, MPH\*

# Language Outcomes (2022)

- Prospective study of 408 children in “Pathways in ASD”
  - Enrolled at time of ASD diagnosis (~2-5 years)
  - Followed longitudinally up to age 10-11
- 22% had a language loss per the ADI-R
- Developmental trajectories were similar between regressed and nonregressed groups
- By age 10, those with a language regression had a ~3-month delay in language skills compared to those without language regression
- Diminished impact on outcomes with rising overall skills

The Journal of Child  
Psychology and Psychiatry



**Predictors of language regression and its association with subsequent communication development in children with autism**

Andrew Pickles, Nicola Wright, Rachael Bedford, Mandy Steiman, Eric Duku, Teresa Bennett, Stelios Georgiades, Connor M. Kerns, Pat Mirenda, Isabel M. Smith, Wendy J. Ungar, Tracy Vaillancourt, Charlotte Waddell, Anat Zaidman-Zait, Lonnie Zwaigenbaum, Peter Szatmari, Mayada Elsabbagh ✉, Pathways in ASD Study Team ... [See fewer authors](#) ^

# Regression in SPARK (2015-2021)

- Dependent adults
  - Language: 31% (~2.4 years); 63% had language return
  - Social: 20%
  - Play: 13%
  - Development: 16%

} ~3.6 years; 33% had other skills return
- Children
  - Language: 32% (~1.9 years); 65% had language return
  - Social: 16%
  - Play: 11%
  - Development: 15%

} ~2.9 years; 34% had other skills return



## SPARK SNAPSHOT

Report 1: UPDATED | Data from Dec 2015 - Jun 2021

# Return of Skills vs. Persistent Loss

- **Duration of regression— ~2-2.5 years**
  - Language: 23.9 months (full criteria loss), 21.4 months (subthreshold criteria loss)
  - Other skill: 29.9 months (full criteria loss), 29.8 months (subthreshold criteria loss)
- **Most regained lost skills— 92% for language, ~66% for other skills**
  - Language loss still present: 7.4% (full criteria), 7.5% (subthreshold criteria)
  - Other loss still present: 32.1% (full criteria), 36.0% (subthreshold criteria)
- **Few experienced progressive loss— < 1% for language or other skills**
  - Progressive language loss: 0.3% (full criteria), 0.5% (subthreshold criteria)
  - Progressive other loss: 0.7% (full criteria), 0% (subthreshold criteria)

Volume 8, Issue 7, July 2015  
ISSN 1750-1907

Research in  
Autism Spectrum  
Disorders



Developmental regression among children with autism spectrum disorder: Onset, duration, and effects on functional outcomes

Robin P. Goin-Kochel<sup>a,\*</sup>, Amy N. Esler<sup>b</sup>, Stephen M. Kanne<sup>a,1</sup>, Vanessa Hus<sup>c</sup>

# Regression Outcomes and Intervention

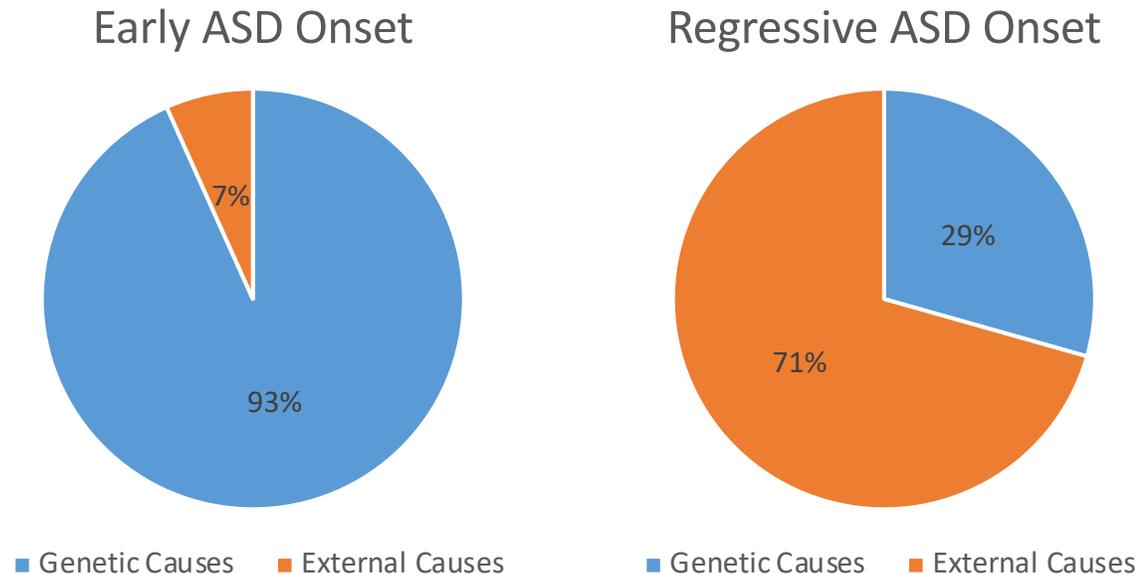
- Possible that immediate, intensive intervention for those with regression could mitigate skill loss and/or effects of skill loss
- Focus on those who do not regain skills or show progressive declines
  - Causal mechanisms may differ
  - Medical workup
  - Type/intensity of interventions
  - Level of support needed



## 2. Regression Influences Caregiver Perceptions About ASD

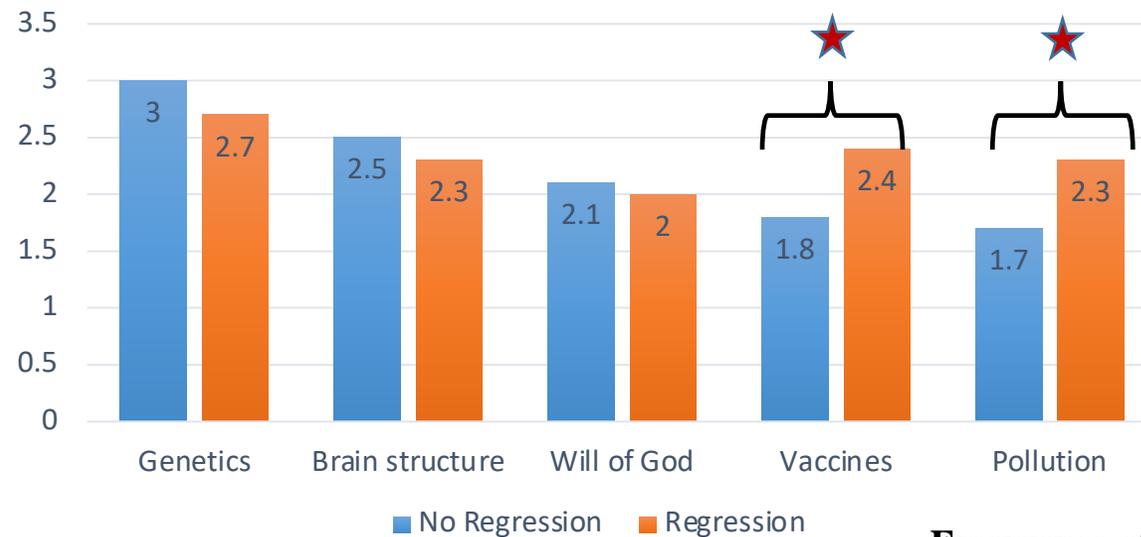
- When caregivers perceive that their child has experienced regression, this can affect how they think about ASD and subsequent decisions they make on behalf of their children and families

- Beliefs about **causes** of ASD
- Treatment** selection



# ASD Onset and Beliefs About Causes

- Examined caregiver reports of ASD onset and endorsement of 21 possible causes of ASD
- 35.3% of children experienced some type of regression during ASD onset
- Causes endorsed by > 25% of the sample
  - Genetics, child's brain structure, will of God, toxins in vaccines, environmental pollution



## Emergence of Autism Spectrum Disorder in Children from Simplex Families: Relations to Parental Perceptions of Etiology

Robin P. Goin-Kochel · Sarah S. Mire · Allison G. Dempsey

# Implications: Beliefs about Causes of ASD

- Caregivers who report regression in their children with ASD are more likely to believe that vaccines played a causal role in their development of ASD
- Could this lead to vaccine hesitancy, delay, and refusal of childhood vaccines?
- Retrospective matched cohort study of 3,729 children with ASD and their younger siblings (Zerbo et al., 2018)
  - Children with ASD were undervaccinated for recommended vaccines between ages 4-6
  - Younger siblings of children with ASD were undervaccinated for recommended vaccines at all ages
  - Children with ASD and their younger siblings are at increased risk for vaccine-preventable diseases
- No examination of influence of regression on vaccination practices

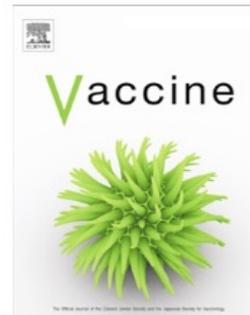
## Vaccination Patterns in Children After Autism Spectrum Disorder Diagnosis and in Their Younger Siblings

**JAMA Pediatrics**

Ousseny Zerbo<sup>1</sup>, Sharareh Modaressi<sup>1</sup>, Kristin Goddard<sup>1</sup>, Edwin Lewis<sup>1</sup>, Bruce H Fireman<sup>1</sup>, Matthew F Daley<sup>2</sup>, Stephanie A Irving<sup>3</sup>, Lisa A Jackson<sup>4</sup>, James G Donahue<sup>5</sup>, Lei Qian<sup>6</sup>, Darios Getahun<sup>6</sup>, Frank DeStefano<sup>7</sup>, Michael M McNeil<sup>7</sup>, Nicola P Klein<sup>1</sup>

# Regression and Vaccine Receipt (2016)

- Examined parent-reported vaccination history and ASD onset in 2,755 SSC children
  - 6 recommended childhood vaccines
  - Early onset, plateau, delays + regression, regression only
- If there was an association between vaccines and ASD onset, we should observe more vaccine receipt in children with a history of regression
- Vaccine receipt was equivalent across all ASD-onset groups
- Children with regression did not receive more vaccines than those without regression
- No evidence of a link between ASD onset and childhood vaccines

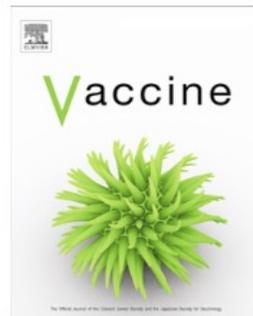


Parental report of vaccine receipt in children with autism spectrum disorder: Do rates differ by pattern of ASD onset?

Robin P. Goin-Kochel <sup>a, b</sup> ✉, Sarah S. Mire <sup>c</sup>, Allison G. Dempsey <sup>d</sup>, Rachel H. Fein <sup>c</sup>, Danielle Guffey <sup>e</sup>, Charles G. Minard <sup>e</sup>, Rachel M. Cunningham <sup>f</sup>, Leila C. Sahni <sup>f</sup>, Julie A. Boom <sup>a, f</sup>

# Regression and Vaccine Hesitancy (2020)

- Examined vaccine hesitancy and associated factors among 225 families in SPARK
- 29% of parents were vaccine hesitant
- Children of vaccine-hesitant parents were more likely to
  - Not be first born
  - Have greater ASD-symptom severity
  - Have experienced **regression** or a **developmental plateau**



## Beliefs about causes of autism and vaccine hesitancy among parents of children with autism spectrum disorder

Robin P. Goin-Kochel<sup>a,b,\*</sup>, Eric Fombonne<sup>c</sup>, Sarah S. Mire<sup>d,e</sup>, Charles G. Minard<sup>f</sup>, Leila C. Sahni<sup>g</sup>, Rachel M. Cunningham<sup>g</sup>, Julie A. Boom<sup>a,g</sup>

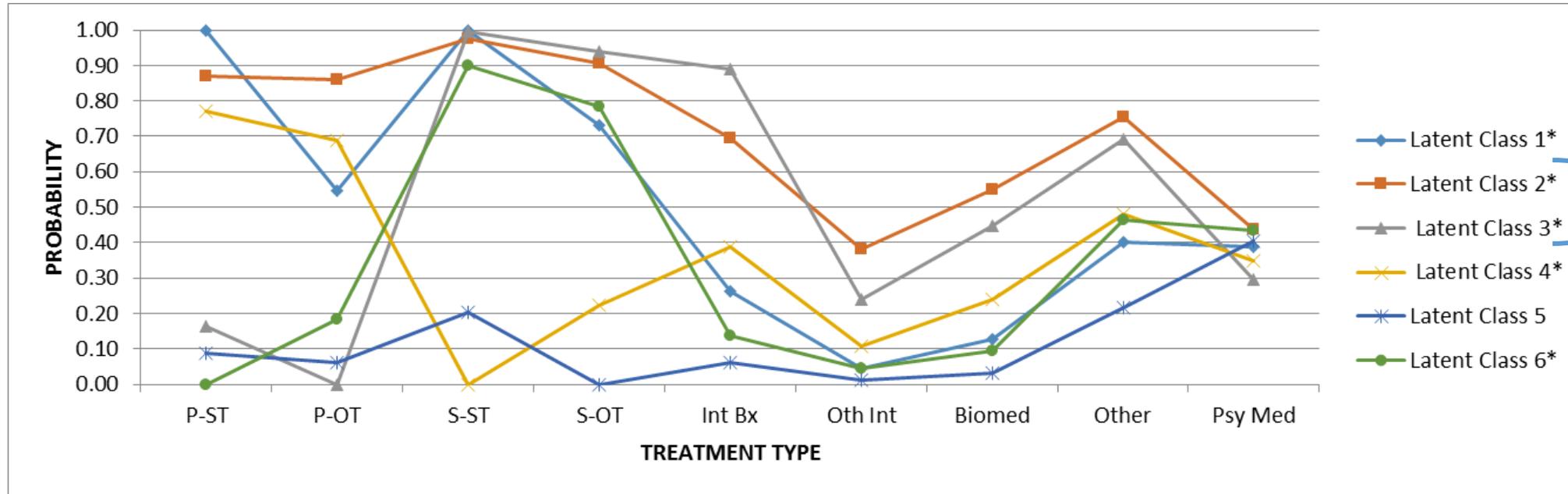
# Implications: Treatment Selection

- Endorsement of environmental agents/toxins as the cause for ASD may lead to use of potentially harmful, detoxifying regimens (e.g., chelation)
- Among Simons Simplex Collection (SSC) families, 44.7% of children with a history of regression reportedly never used early intensive behavioral intervention
- 34.7% with a history of regression had used biomedical/alternative treatments compared to 19.8% of those with no skill loss
- Opportunity to educate families on evidence-based interventions and allocate resources to those with greatest potential benefits

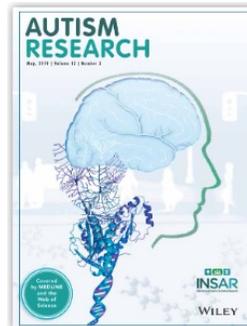


# Treatment-use Groups and Regression (2019)

- Examined lifetime treatment use among 2,582 SSC families



> 40% regression



Using latent class analysis to identify treatment-use subgroups among parents of children with autism spectrum disorder

Sarah S. Mire ✉, Samuel McQuillin, Madeline Racine, Robin P. Goin-Kochel

# Conclusions (2019)

- Parents of children with a history of regression may be trying “anything and everything” to rescue lost skills or bring development back to pre-loss levels
- Many different treatments may be used if little or no progress is seen
- Classes 2 and 3, which had the highest proportion of regressed cases, had the highest probability of biomedical/alternative treatment use
- Potential concern about therapeutic investment—too much alternative treatment, not enough intensive behavioral intervention

# 3. Regression as a Clue to Causes of ASD

- Onset of ASD varies across individuals
  - Some experience delays and early signs in the first year
  - Others have a later or slower symptom onset
- Either may include a regression
  - Acute
  - Gradual
- As with ASD, regression is heterogeneous
- Understanding the **timing** and **nature** of skill loss may reveal clues related to the cause of ASD
- Biochemical understanding of regression is limited

# Factors Potentially Related to Regression in ASD

- Abnormal **brain enlargement** among affected preschool-aged males (Nordahl et al., 2011)
- Increased rates of **seizures** (Zhang et al., 2012)
- Family history of **autoimmune thyroid disease** (Molloy et al., 2006)
- Family history of **neuropsychiatric disorders** (Zhang et al., 2012)



# Likely Gene-Disrupting (LGD) Mutations

- Changes that likely alter the function of the gene
- Focused on participants from the Simons Simplex Collection (SSC)
- *Is regression more common in children with ASD + LGD mutations?*
- Examined mutations from five distinct LGD classes
- Participants classified as regressed or not based on retrospective interview (ADI-R)

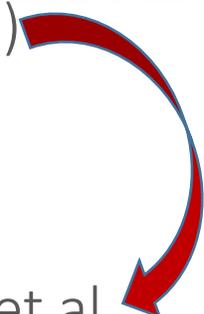
Published in final edited form as:

*Neuron*. 2012 April 26; 74(2): 285–299. doi:10.1016/j.neuron.2012.04.009.

## **De Novo Gene Disruptions in Children on the Autistic Spectrum**

Ivan Iossifov<sup>1,6</sup>, Michael Ronemus<sup>1,6</sup>, Dan Levy<sup>1</sup>, Zihua Wang<sup>1</sup>, Inessa Hakker<sup>1</sup>, Julie Rosenbaum<sup>1</sup>, Boris Yamrom<sup>1</sup>, Yoon-ha Lee<sup>1</sup>, Giuseppe Narzisi<sup>1</sup>, Anthony Leotta<sup>1</sup>, Jude Kendall<sup>1</sup>, Ewa Grabowska<sup>1</sup>, Beicong Ma<sup>1</sup>, Steven Marks<sup>1</sup>, Linda Rodgers<sup>1</sup>, Asya Stepansky<sup>1</sup>, Jennifer Troge<sup>1</sup>, Peter Andrews<sup>1</sup>, Mitchell Bekritsky<sup>1</sup>, Kith Pradhan<sup>1</sup>, Elena Ghiban<sup>1</sup>, Melissa Kramer<sup>1</sup>, Jennifer Parla<sup>1</sup>, Ryan Demeter<sup>2</sup>, Lucinda L. Fulton<sup>2</sup>, Robert S. Fulton<sup>2</sup>, Vincent J. Magrini<sup>2</sup>, Kenny Ye<sup>3</sup>, Jennifer C. Darnell<sup>4</sup>, Robert B. Darnell<sup>4,5</sup>, Elaine R. Mardis<sup>2</sup>, Richard K. Wilson<sup>2</sup>, Michael C. Schatz<sup>1</sup>, W. Richard McCombie<sup>1</sup>, and Michael Wigler<sup>1,\*</sup>

# LGD Mutations and Regression

- Mutations in embryonically expressed genes (early) < likely to have regressed (0%)
  - Mutations in postsynaptic density genes (later) > likely to have regressed (36%)
  - Mutations in essential genes (required) > likely to have regressed (29%)
  - Abnormal **brain enlargement** among affected preschool-aged males (Nordahl et al., 2011)
    - Decreased synaptic pruning has been associated with increased head size (Courchesne et al., 2011; Pierce & Eyster, 2011)
- 

---

Published in final edited form as:

*J Autism Dev Disord.* 2017 November ; 47(11): 3600–3607. doi:10.1007/s10803-017-3256-4.

## **Gene Disrupting Mutations Associated with Regression in Autism Spectrum Disorder**

**Robin P. Goin-Kochel<sup>1,2,\*</sup>, Sandy Trinh<sup>3</sup>, Shelley Barber<sup>3</sup>, and Raphael Bernier<sup>4,5,\*</sup>**

# Genetics and Regression (2019)

- Strong evidence for genetic mechanisms in ASD (<https://gene.sfari.org/>)
- 16/86 genes associated with ASD showed evidence of cases with regression
  - 11 with consistent evidence: *ADNP, CHD2, CHD8, CNTNAP2, GRIN2B, KMT5B, MECP2, NRXN1, SCN2A, SHANK3, SYNGAP1*
  - 5 with few case reports: *ANKRD11, ASH1L, DEAF1, PTEN, TRIP12*
- These genes are implicated in transcriptional and synapse regulation
- Genome-wide studies are needed to identify genetic loci associated with regression
- Comprehensive reports of genetic-expression patterns for identified genes and their timing

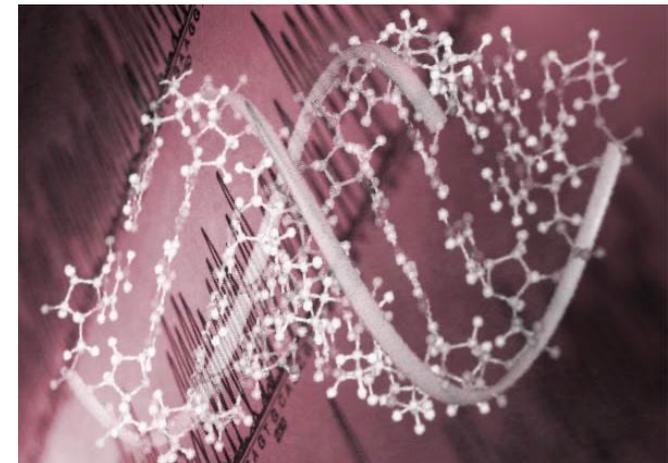


**Genetic mechanisms of regression in autism spectrum disorder**

**Kristiina Tammimies**

# Future Directions in the Genetics of Regression

- Examine prevalence of regression in individuals with genetic copy number variants (CNVs) associated with ASD
  - 16p11.2, 1q21, 15q13.3
- Focused study on regression in other conditions
  - Rett Syndrome
  - Landau-Kleffner Syndrome
  - Epilepsy with continuous spike and wave during sleep (CSWS)
- Epigenetic and gene-environment interactions associated with regression



# What should you do if you suspect regression in your child?

- Notify your child's pediatrician
  - Neurologist, geneticist, developmental pediatrician, psychologist
- Provide concrete examples of skills lost or in decline
  - Brief videos
- Referral to neurologist
- Course of action depends upon current age of the child, biological sex, medical background, degree/length of the regression
- Workup may include MRI (brain differences), lumbar puncture (CNS disorders), EEG (seizures/sleep disorders), genetic testing (genetic syndromes)
- Notify your child's therapists/teachers

# Take Home Messages

- Regression is common in ASD
  - ~1/3 experience skill loss based on retrospective reports
  - Most experience a progressive decline in skills based on prospective reports
  - Part of ASD onset
- Regression is heterogeneous (many “flavors”)
- Regression may influence how caregivers view and manage ASD
- No link between regression and vaccines
- Research on regression is limited by
  - Lack of consensus on a definition
  - Standardized tools to measure regression
- Talk to a healthcare provider if you suspect regression in your child

# Stay Connected with the Kochel Lab

[www.bcm.edu/autism](http://www.bcm.edu/autism)



[www.facebook.com/KochelLab](https://www.facebook.com/KochelLab)



- Robin Kochel, Ph.D., [kochel@bcm.edu](mailto:kochel@bcm.edu)
- Kochel lab, [asdresearch@bcm.edu](mailto:asdresearch@bcm.edu)