

## An Autism Update: Relationship to Vaccines? Increasing Incidence?

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### Contents

- Autism Characteristics
  - History of Autism
  - Current Epidemiology/Prevalence
  - Past/Current Causation Theories
  - Characteristics
  - Evaluation
  - Treatment
- Why is there increasing incidence
- Is it associated with vaccinations

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### Autism History

- Initially described in 1943 by Leo Kanner
  - "Autistic Disturbances of Affective Contact"
  - 11 patients (8 male)
  - Three patterns noted
    - "Extreme autistic aloneness"
    - Delayed echolalia
    - Resistance to change
- 50's-60's
  - Early childhood schizophrenia
- 70's
  - Biologic in origin, c/w MR

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### DSM-5 Autism Criteria

- Released 5/2013
- 91% retain diagnosis of ASD vs. DSM-IV
- Separates ASD into two disorders (Autism, SCD)
  - Persistent impairment in reciprocal social communication
  - Restricted, repetitive patterns of behavior
  - Needs to be present early, cause impairment
- Removes Asperger's, PDD-NOS, other sub-categories
  - Should be evaluated for Social (Pragmatic) Communication Disorder

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### DSM-5

- Autism Spectrum Disorder
  - Social communication/interaction deficits
    - Reciprocity (sharing of interests, emotions, affect)
    - Nonverbal communication (eye contact, gestures)
    - Relationships (imaginative play, friends)
  - Restrictive/repetitive behaviors, interests, activities
    - Movements (stereotypies, echolalia, lining up toys)
    - Resistance to change (routine, food)
    - Fixed interest
    - Hyper/hypo reactivity to sensory input (pain, temperature, sounds, textures, lights, movement)
- Severity graded 1 - 3 based on required support

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### Autism Epidemiology

- Incidence currently 1/59 (16.8/1000) of 8 year olds (2014)
- 2-18% concordance in siblings
- 10 - 31% concordance in fraternal twins
- 36-95% concordance in identical twins
- Average age of diagnosis = 52 months
  - Can be reliably diagnosed at 2 yo
  - 44% of diagnoses made before age 3 yo
  - Minorities are diagnosed later
- Positive correlation with socioeconomic status

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### Autism Epidemiology

- Dramatic gender difference
  - Males - 1/37
  - Females - 1/151
- Varies by race (less so now)
  - Caucasians - 1/63
  - Blacks - 1/81
  - Hispanic - 1/93
  - Could be a function of testing
- Majority do not have MR
  - Caucasians - 25%, Blacks - 48%, and Hispanics - 38%

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### Autism Epidemiology

- Non-hispanic caucasian children were 30% more likely than non-hispanic black children to get diagnosis
- Non-hispanic caucasian children were 50% more likely than hispanic children to get diagnosis
- 31% had IQ <70
- 25% had 70 < IQ < 85
- 44% had IQ > 85

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### Autism Cause

#### Prior Theories of Etiology (Discredited)

- Inherited emotional disturbance (1943)
- Eveloff (1960) - cold, detached ritualistic parents
  - Refrigerator moms (Bettelheim in 1967)
    - Withholding of affection
    - Rates of cure (85%) were fraudulent
- Mercury (Methylmercury, not ethylmercury)
  - No increase with high fish consumption (mercury)
- Vaccines (Will discuss this later)

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## Autism Cause

- Three factors
  - Genetics
    - Twin studies show it is at least 40%
  - Immunological
  - Environmental

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## Autism Genetics

- Definitely not Mendelian
  - Possibly polygenetic
  - Possibly epigenetic
- No consistent risk locus in multiple studies
- Possibly caused by a multitude of genetic alterations that impact limited pathways of brain development and plasticity.
- Likely a result of de novo mutation in sperm or egg

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## Autism Genetics

- Minority associated with other disorder (10%)
  - Tuberous Sclerosis
  - Fragile X
  - 15q abnormalities
  - Rett syndrome
  - SLO
  - Downs
  - Mitochondrial

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### Autism Genetics

- Genetic structural variation contributes significantly (copy number variations)
- Increase in de novo nonsense variations in autistic patients
- Transcriptome is different

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### Genetic Testing

- Three types of genes implicated
  - Enzymes that influence when specific genes turn on or off during brain development.
  - Genes that govern synapses, the gaps between nerve cells that control whether a nerve signal travels forward.
  - Genes that regulate how other genes are translated into proteins

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### Autism Genetics

- Common and rare variants contribute to ASD by modification of neuronal networks
- A second hit may be necessary
- Intellectual Disability
  - Common genetic basis or
  - Poor intelligence unmasks poor communication

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## Autism Genetics

### Why More Common in Males

- Three theories
  - Female Protective effect
    - More extreme genetic mutations are required for a girl to develop autism than for a boy
  - Extreme Male Brain Theory
    - Higher levels of fetal testosterone explain the increased prevalence of autism spectrum disorders among males
  - Female under diagnosis (ascertainment bias)
    - 2017 meta-analysis said that ratio was 4.2:1 for 54 studies
      - Only 3.25:1 if the researcher actually did assessment (not from records)
    - Females have same severity as males
      - Less externalizing behavior (ADHD, aggressivity)
      - Relatively higher levels of social ability at baseline

Loomes R, Hull L, Mandy WPL. What is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. Journal of the American Academy of Child & Adolescent Psychiatry (2017). doi: 10.1093/aacp/aww103

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## Epigenetics

- Do not impact the DNA, rather the gene expression
- DNA methylation
- MECP2 mutation
  - Reader of Epigenetic information and modulator of chromatin architecture
- Folate-methionine pathway enzymes
  - Methyl donor for methylation
- Histone acetylation
- Chromosome remodeling
  - Changes in chromatin structure or protein
    - Changes gene expression

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## Autism

### Immune Dysfunction

- T-cell dysfunction
- Increased autoantibody production
- Increase in activated B and NK cells
- Increase in proinflammatory cytokines in serum and CSF
- Evidence of microglial and astroglial activation

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### Autism Causes

- Autoimmune Diseases
  - Infectious etiology (usually in-utero)
    - In-utero or ex-utero
    - Rubella, CMV
  - Autoantibodies target brain
    - Could be due to environmental trigger
  - Meta-analysis in 2015 found children with a family history of autoimmune disease were more likely to have autism
  - With maternal autoimmune disease, antibodies could cross the placenta and contribute to ASD

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### Autism Causes

- GI connection
  - Very common in autistic individuals
  - GI inflammation, IgE or cell mediated food allergies, gluten-related disorders, visceral hypersensitivity, dysautonomia and GERD may be mechanism for linkage
  - May be linked by neural connections or immunology
    - Gut-brain axis
  - Leaky gut theory
    - Not well supported
    - In mice, normalization of intestinal barrier resulted in better behavior
    - Neuroactive opioid peptides can leak into blood, causing ASD

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### Autism Cause Environmental Associations

- Advanced Parental Age
  - Men > 50
    - with daughter 1.79x to have autistic grandchild
    - with son 1.67x to have autistic grandchild
  - Fathers > 50 were 2.2x more likely to have autistic children than fathers <30
  - Monotonic association between increasing parental age (mothers, fathers), risk of autism
    - .18% for each 5 years maternal, .11% paternal
    - Cross term needed in regression

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**Autism Cause**  
**Environmental Associations**

- Pollution
  - There is a 3-9% increase in odds of autism per interquartile range increase in pregnancy exposure to NO and NO<sub>2</sub>
    - California study
- Increase with exposure to medications
  - Valproate is associated with higher incidence (2.9 HR)
  - Folate results in lower incidence
  - Maternal antidepressant use (SSRIs)
- Other agents – paracetamol, thalidomide, misoprostol

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**Autism Cause**  
**Environmental Associations**

- Increased incidence (60%) if mother is near pesticide treated field (North Carolina study)
  - Worse if in third trimester
- IVF is not associated with increased autism
- Preterm birth (<2000 g) is associated with a 5% rate
- Vitamin D deficiency has been postulated
- Maternal abuse during childhood
- Maternal stress, gestational DM
  - Parental migration results in increased incidence

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**Autism Cause - Other**

- Associated with shorter (<18 months), or longer (>60 months) interpregnancy interval
- Associated with maternal and GDM
- Associated with L&D complications

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### Autism Causes

- Endogenous opiate precursor theory
  - Injections of small amounts of opiates can induce autistic symptoms.
  - Theory is that opioids produced through casein or gluten metabolism leak through a leaky gut, and impact neurotransmission, brain maturation, behavior, attention, communication, and social/cognitive functioning
  - Studies have found an increased level of opiates in CSF of autistic individuals

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### Autism Cause

#### Pathological correlates

- Neural based deficits in recognizing/understanding speech
- Decreased numbers of Purkinje cells in cerebellum
- Opioids may be involved
  - Stereotypies can result
  - Higher level in autistic children
  - Higher autism incidence in mothers prescribed before preg
- Functional MRI shows abnormal connectivity
- PET shows serotonin synthesis abnormalities
- Brain electrophysiology shows delay in processing of eye gaze

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### Autism Cause

- Breaking Research
  - Autistic brains have abnormal connectivity
  - Associated with decrease pruning of synapses
    - Inhibit insulin receptors
  - Involves MHC1
    - Also involved in immune system function
- Study to Explore Early Development (SEED)

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### Autism Characteristics

- Impaired ability to use or understand non-verbal behaviors
- Autistic Patients do not develop peer relations
- Lack joint attention
- Do not have social/emotional reciprocity
- Sensory perception is aberrant
- Stereotypies

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### Autism Stereotypies

- Stereotypies (37-95% of individuals)
  - Self stimulating/self injurious
- Examples
  - Hand flapping
  - Rocking
  - Swaying
  - Dipping
  - Walking on tip-toes
  - Circling
  - Head banging
  - Slapping
  - Biting
  - Pinching

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### Autism Characteristics

- Delay and deviations in language development
- Restricted, repetitive, and stereotyped patterns of behavior
  - Inflexible adherence to rituals/routines
    - Certain foods, routes to school
- Preoccupation with stereotyped/restricted patterns of interest
- Persistent preoccupation with parts of toys (wheels)
- Sensitivity to various textures (foods, clothing)

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### Autism Characteristics

#### Language

- 2/3rds have language delay by 2 years of age
- 1/4th to 1/3rd achieve early language milestones, but then have regression
- Impaired social interaction is the hallmark of autism
- 67% eventually have useful speech

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### Autism Characteristics

- 2/3rds between 6 and 15 yo experience bullying
- 28% have self-injurious behaviors
  - Head banging
  - Arm biting
  - Skin scratching
- About 50% will bolt or wander
  - Leads to drowning as a major cause of death
- Many comorbid conditions
  - Next slide
- Average life span – 36 years

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### Autism Associations

Characteristic	Autism	Control
Epilepsy	20-33%	1-2%
Chronic GI problems	9-91%	9-37%
Disturbed sleep	40-86%	20-43%
Feeding issues	70% (36% severe)	
ADHD	30-61%	6-7%
Anxiety	11-42%	3% children, 15% adults
Depression	7% children, 26% adults	2% children, 7% adults
Schizophrenia	4-35%	1.1%

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### Additional Autism Associations

- 25% have learning difficulties
- 31% have intellectual disability
- 28% self-injure
- 33% are non- or minimally verbal
- 50% have dyspraxia
- 50% have language delay
- Drowning is major cause of death

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### CDC Screening Recommendations

- Developmental delays/disabilities
  - 9 months
  - 18 months
  - 24 or 30 months
  - More if high risk (e.g. preterm, low birth weight)
- Autism specific screening
  - 18 months
  - 24 months

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### Autism Red Flags

- Deficits in social skills
- Deficits in language, behavior
- Frequent tantrums, intolerance to change
- No babbling by 9 months
- No pointing/gestures by 12 months
- Doesn't know name by 12 months
- No words by 16 months
- No pretend/symbolic play by 18 months
- No two word phrases by 24 months
- Regression of language skills at any age

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### Autism Evaluation Medical Testing

- Genetic testing
- Neuroimaging
- EEG
- Metabolic screening

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### Genetic Testing

- Karyotype is outdated?
  - 3% detection
  - Specifically for balanced translocation (>2 miscarriages)
- Chromosomal microarray (comparative genomic hybridization)
  - 8% detection
  - Not necessarily recommended
  - Specific panels are available
- Xpanded Autism/ID panel - GeneDx
- Whole Exome sequencing
  - Whole genome sequencing is available, but still expensive
- Fragile X is separate
  - Look for other characteristics
- MECP2 for typical Rett presentation
- Methylation study for Angelman
- PTEN if macrocephaly

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### Neuroimaging

- AAP recommendation: only for those with
  - Regression
  - Microcephaly
  - Midline defects
  - Neurocutaneous lesion
  - Abnormal neurologic exam
- fMRI
  - Shows disrupted neural circuits
    - Result of genetic mutations resulting in abnormal migration, organization, and circuits
- DTI
  - Distinct white matter fiber tract maturation

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### Electroencephalogram

- Connection with Landau-Kleffner
- Frequently will have epileptiform activity (60%)
  - Not necessarily seizures (20%)
- Not recommended by AAP unless regression, behavior change, clinical seizures or possible subclinical seizures

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### Metabolic Testing

- Should not be routinely performed unless
  - Cyclic vomiting
  - Hypotonia
  - Lethargy
  - Poor growth
  - Unusual odor
  - Other organ involvement
  - Ataxia/movement disorder
  - Evidence of storage disease

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### Metabolic Testing

- Testing can include:
  - Lactate
  - Pyruvate
  - Carnitine
  - Acylcarnitine profile
  - LFTs
  - BUN, Creatinine
  - Serum Amino Acids
  - PKU testing
  - Urine organic acids

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## Autism Evaluation

- Diagnostic instruments
  - Parental reporting
    - Autism behavior checklist (ABC)
    - Gilliam autism rating scale (GARS-2)
    - Autism Diagnostic interview-revised (ADI-R)
    - Modified checklist for autism in toddlers (M-CHAT-R/F)
  - Direct observation
    - Childhood autism rating scales (CARS)
    - Autism diagnostic observation schedule – Generic (ADOS-G)
    - Screening Tool for **Autism** in Toddlers & Young Children (STAT)

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## M-CHAT Questions

- Does your child enjoy being swung, bounced on your knee, etc.?
- Does your child take an interest in other children?
- Does your child like climbing on things such as stairs?
- Does your child enjoy playing peek-a-boo/hide-and-seek?
- Does your child ever pretend, for example, to talk on the phone or take care of a doll or other pretend things?
- Does your child ever use an index finger to point, to ask for something?
- Does your child ever use an index finger to point, to indicate interest in something?
- Can your child play properly with small toys (e.g. cars or blocks) without just mouthing, fiddling, or dropping them?
- Does your child ever bring objects over to you (parent) to show you something?
- Does your child look you in the eye for more than a second or two?
- Does your child ever seem oversensitive to noise? (e.g., plugging ears)
- Does your child smile in response to your face or your smile?

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## M-CHAT Questions

- Does your child imitate you? (e.g. If you make a face, will your child do so?)
- Does your child respond to his/her name when you call?
- If you point at a toy across the room, does your child look at it?
- Does your child walk?
- Does your child look at things you are looking at?
- Does your child make unusual finger movements near his/her face?
- Does your child try to attract your attention to his/her own activity?
- Have you ever wondered if your child is deaf?
- Does your child understand what people say?
- Does your child sometimes stare at nothing or wander with no purpose?
- Does your child look at your face to check your reaction when faced with the unfamiliar?

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## MCHAT Available En Espanol

**CUESTIONARIO DEL DESARROLLO COMUNICATIVO Y SOCIAL EN LA INFANCIA (MCHAT)**  
 MCHAT, validado con un estudio, lo asegura que le parece que refleja mejor cómo su hijo o hija actúa  
 que los otros cuestionarios de desarrollo que usted podría usar. Se lo puede usar en los niños con una o dos veces el nivel de edad que se indica. Por favor, conteste a todas las preguntas.  
 Si su hijo o hija tiene un diagnóstico de "Autismo" o "Trastorno del Espectro del Autismo", conteste con un "No".  
 1. ¿Le gusta hablar a otros como por ejemplo, amigos, familiares, juegos del parque...? Si No  
 2. ¿Le gusta jugar con otros niños o niñas? Si No  
 3. ¿Le gusta que el adulto juegue con el niño al "imitar" (copiar los otros y luego Si No  
 4. ¿Le gusta jugar a escondite o jugar con bloques de madera? Si No  
 5. ¿Alguna vez ha jugado con otros niños o niñas en el patio, un parque, un jardín, un jardín de niños, como el centro de día de un niño o una escuela, como el centro de rehabilitación un niño o una niña?  
 Si No  
 6. ¿Puede señalar con el dedo para pedir algo? Si No  
 7. ¿Puede señalar con el dedo para mostrar que algo le gusta o le interesa? Si No  
 8. ¿Puede jugar de imaginación con otros niños o niñas pequeños (por ejemplo, cochitos, Si No  
 muñecas, bloques de construcción) sin necesariamente hablar, jugar o interactuar?  
 Si No  
 9. ¿Puede hacer imitaciones por imitación? Si No  
 10. ¿Le gusta mirar a los ojos cuando otros hablan? Si No  
 11. ¿Puede dar la mano o saludar a un adulto cuando se despiden? Si No  
 12. ¿Puede imitar o repetir gestos o acciones que usted hace? (por ejemplo, Si usted hace una Si No  
 rima al cantar canciones de bebé)  
 Si No  
 13. ¿Se queda cuando se le llama por su nombre? Si No  
 14. ¿Se queda cuando se le llama para un momento? Si No  
 15. Si usted vive con otros niños o niñas en la habitación... ¿Algunos de los niños o niñas Si No  
 le miran cuando usted habla?  
 Si No  
 16. ¿Ha aprendido a hacer cosas que otros niños o niñas le enseñan a hacer? Si No  
 17. ¿Usted está interesado en jugar con otros niños o niñas?  
 Si No  
 18. ¿Pasa su hijo o hija mucho tiempo con los dedos por su nariz, averiguando a los ojos? Si No  
 19. ¿Pasa su hijo o hija mucho tiempo con los dedos por su boca, averiguando a los ojos? Si No  
 20. ¿Alguna vez ha pensado que su hijo o hija podría estar sordo? Si No  
 21. ¿Alguna vez ha pensado que su hijo o hija podría estar ciega? Si No  
 22. ¿Alguna vez ha pensado que su hijo o hija podría tener una discapacidad? Si No  
 23. ¿Su hijo o hija tiene que enfrentarse a una situación desconocida, le está primero a usted Si No  
 o le está primero a otros niños?  
 Si No  
 © 2011 Diana Rethem, Deborah Fox, & Marlene Burton

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## Additional Ancillary Autism Testing

- Audiometry
- Vision checking
- Developmental testing
- Neuropsych testing
- Sensimotor/Occupational therapy testing
- Lead testing

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## Steps if Autism Screening Positive

- Parental education
- Referral to center (Child development unit)
- Developmental Services
  - Early intervention < 3 yo
  - Public school system > 3 yo
- Genetic counseling
  - Risk of subsequent children having autism – 2-8%
- Medical Evaluation
- Monitoring/support
  - Families as well

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### Autism Treatment

- Behavioral Intervention
- Pharmacologic Intervention
- Other Therapy
  - Occupational
  - Speech
  - Physical
  - Sensory Integration

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### Applied behavior analysis

- Encourages socially significant behaviors through a reinforcement learning technique that trains children with autism to engage in activities of daily living.
- Discrete trial training (DTT) methodology is the most widely recognized form.
  - teaches attention, compliance, imitation, and discrimination learning as small, individually acquired tasks.
- Best theory for severely impacted patients, maybe not for less impacted
- Cost as much as 40-60K/year

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### Autism Pharmacology

- Use educational, behavioral interventions first
- Target various symptoms/behaviors
  - Hyperactivity
  - Disruptive behaviors
  - Repetitive behaviors/rigidity
  - Anxiety
  - Depression
  - Mood lability

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**Autism Pharmacology**  
**Additional Therapies**

- Seizures
  - AEDs
- GI Problems
  - Miralax
- Sleep
  - Melatonin, Niaprazine, Clonidine
- Parasomnias
  - Clonazepam, TCAs

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**Autism**  
**Complementary Therapies**

- 28%-75% use complementary/alternative medicine
  - 17% special diets
  - Few are proven effective in clinical trials
- Hypotheses
  - GI abnormalities – leaky gut
    - Use secretin, probiotics, antifungals
  - Food sensitivities
    - Gluten free diets, Casein free diets; No evidence of benefit
  - Autoimmunity
    - Immunotherapy
  - Metabolic abnormalities
    - Antioxidants
  - Heavy metal toxicity
    - Chelation
  - Nutritional imbalances
    - Supplements

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**Autism**  
**Complementary Therapies**

- Melatonin – Sleep hormone – May benefit
- Secretin – GI hormone – No evidence
- Omega-3 fatty acids – May have CV benefit
- Gluten-free casein-free diet – Theory is that behaviors in autism are caused by opioid activity resulting from gluten or casein release in gut
  - Possible small impact for particular individuals

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## Autism Treatment Investigational

- Total of 963 studies listed in Clinicaltrials.gov
- Investigational studies include:

CM -At	Lurasidone	EMDR	rTMS	Oxytocin
Stem Cell transplant		Acetyl-cholinesterase inhibitors		Pregnenolone
Transcranial DC stim		Aripiprazole	Hyperbaric Oxygen	
Cannabidiol	Abaclofen	Naltrexone	Atomoxetine	Risperidone
Brexiprazole	N-acetylcysteine	Fecal microbiota transplantation (FMT)		
Memantine	Methylphenidate	Essential oils	Mirtazapine	Melatonin
Tetrahydrobiopterin		D-cycloserine	Milnacipran	DMSA
Gammaflex	Propranolol	Everolimus	Cannabidiol	Acupuncture
Buspirone	Bumetanide	Omega-3 fatty acids		
Mecamylamine	Fluoxetine	Fluvoxamine	Fluconazole	Olanzapine
Methylcobalamin	Citalopram	Riluzole	Clonidine	Ketamine
Human secretin	Vasopressin	Probiotics	Gabapentin	Balovaptan
Sulforaphane	Folinic acid	Lenalidomide	Acamprosate	Minocycline

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## Study of Microbiota Transfer Therapy

- 18 patients
- Antibiotics, bowel cleanse, stomach acid suppressant, fecal microbiota transplant
- Significant improvement in GI symptoms, autism related symptoms, gut microbiota
- Retained effect at 2 years
  - Also retained greater fecal bacterial diversity
    - Bifidobacterium and Prevotella increased
- Problems
  - Not controlled

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## Study of Sulforaphane

- Double-blinded, placebo-controlled
  - 44 men (age 13-27)
    - 26 received sulforaphane for 18 weeks
    - 65% improved vs. 0% in control arm
    - Effect disappeared after 4 weeks

Lynch R, Diggins EL, Connors SL, Zimmerman AW, Singh K, Liu H, Talalay P, Fahey JW. Sulforaphane from Broccoli Reduces Symptoms of Autism: A Follow-up Case Series from a Randomized Double-blind Study. Global Advances in Health and Medicine. 2017 Oct 26.

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**Autism Treatment Professionals**

- Developmental pediatrician
- Pediatric neurologist
- Child psychiatrist
- Psychologist
- Geneticist
- Speech therapist
- Occupational therapist
- Audiologist
- Social worker
- Physical therapist

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**Autism Education Needs**

- Small class size
- Individualized programming
- Trained teachers
- OT, PT, speech
- Assessment and change in curriculum
- Structured environment
- Behavioral training
- Family involvement

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**Is  
Incidence/Prevalence  
of Autism Increasing?**

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### Autism Increase – Why does it Matter?

- Increased resources required
- Implies that there is an environmental factor involved
  - Preventable?

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### Autism Epidemiology Prevalence Increasing

- Increasing prevalence
  - 1990s
    - 1/1000 for autism, 2/1000 for ASD
  - 2000
    - 7/1000
  - 2012 (parental report)
    - Up to 20/1000 for ASD (study dependent) vs. 11.6/1000 in 2007
- US ASD prevalence in 2008 was 11.3/1000
  - 23% increase from 2006
  - 78% increase from 2002
  - New Jersey is highest (1/45), Utah is second, Alabama (1/175).
- Currently at 1/59 (2014) per CDC sample of 11 states in U.S.
  - 1/37 for males, 1/151 in females

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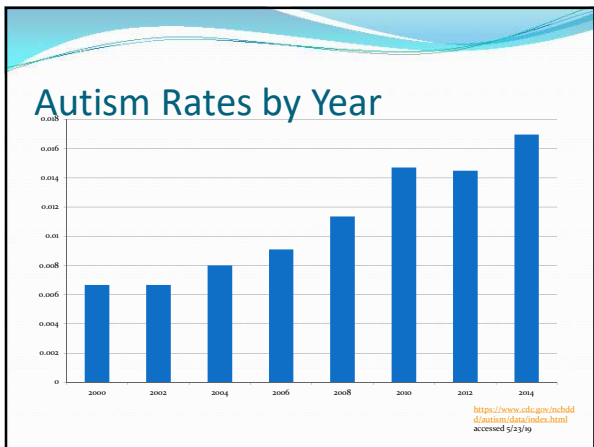
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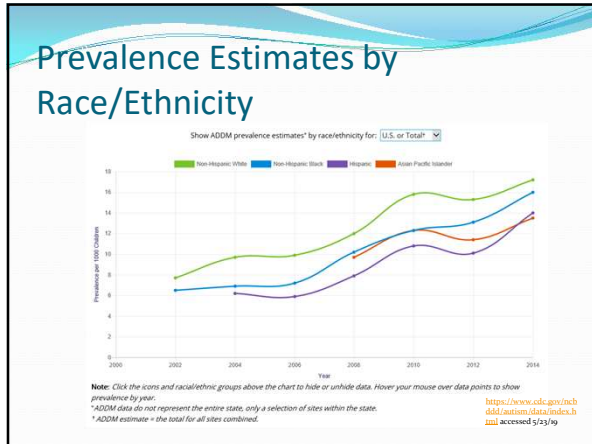
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- ### Methodological Explanation for Increase
- Different diagnostic criteria, methods
    - Specifically addition of Asperger
  - Different sampling procedures for prevalence estimate
  - Increased awareness of parents, professionals
  - Identification in other disorders (Downs)
  - Early, incorrect diagnosis
  - Availability of services, service workers
    - Possibly underestimated previously

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- ### Autism Epidemiology
- #### Prevalence Increasing
- 72% of professional psychologists feel that the prevalence has increased beyond that attributable to methodology

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**Issues that may contribute**

- Environment
  - Nitric oxide
  - Fertilizer
  - Other toxins
- Increased paternal age
- Increased use of medication
- Increased survival of premature babies
- More use of electronics (social isolation)

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**Autism Prevalence Increase**

- My opinion
  - The major portion is attributable to broader definition, better detection/screening
  - Other factors do account for increase
    - Increased paternal age (0.5%)
    - Increased environmental toxins
    - Increased social economic status
    - Low birth weight (<1%)
    - Other?
  - "A true increase can not be ruled out"

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**Reasons for Increase in Prevalence**

- Great controversy has surrounded the so-called "autism epidemic" and whether or not the current rates reflect a true increase in incidence. Some factors believed to contribute to the increased rates include the following:
- Greater awareness of autism in both the medical community and general public has led to increased screening and diagnosis.
- American Academy of Pediatrics recommendations have led to increased screening.
- Broadened definitions - Earlier studies predominantly included those with autistic disorder, while the more recent studies reflect the full spectrum.
- Better Diagnostics - Children who had been diagnosed with other disorders (e.g., intellectual disability, language impairment) in the past are now being diagnosed as having an ASD (this applies to individual children who receive a new diagnosis and also reflects changing diagnostic patterns in the population over time).
- Eligibility for services under the Individuals with Disabilities Education Act (IDEA) - In 1990, autism became a diagnosis for which children became eligible for special education services under the IDEA law.
- There are likely unidentified factors associated with the increase in prevalence. Current epidemiologic studies, such as the Study to Explore Early Development (SEED), are looking at-risk and protective factors. See <https://www.cdc.gov/ncbddd/autism/seed.html> for more information.
- Diagnosis of ASD in children with genetic syndromes that may have associated features of autism.

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**Autism and Vaccinations**

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The number of deaths/year prevented by all vaccines is:

- 10,000
- 20,000
- 40,000
- 1 million

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The number of illnesses prevented by vaccination is

- 30,000
- 60,000
- 90,000
- 500,000
- 20 million

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## Measles incidence prior to vaccine

- Average yearly between 1958-1962
  - Cases - 503,282
  - Related Deaths - 432

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## Autism and Vaccination

- The MMR hypothesis
  - The Andrew Wakefield Controversy
    - Autistic enterocolitis
  - The Hannah Poling Story
- The thimerosal hypothesis
  - Mercury in vaccines
- Spreading out vaccination schedule
  - Overloading the infant's immune system

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The Centers for Disease Control and Prevention (CDC) and the Department of Health and Human Services have reported that the ongoing measles epidemic has, as of 20 June 2019, has resulted in 1077 cases, an increase of 33 cases since the last report. This makes 2019 (which is just short of 6 months old) the worst year for measles since 1992, when there were 963 cases for all 12 months.

At this rate, we can expect well over 2000 measles cases for 2019, making it the worst year since the major measles epidemics of the late 1980s.

In 2000, the CDC had stated that measles was eradicated in the USA. But as a result of fears and misinformation about the MMR vaccine, which protects against measles, mumps, and rubella, vaccination rates have dropped allowing measles to again attack children.

<https://www.skepticalraptor.com/skepticalraptorblog.php/us-measles-epidemic-highest-level-35-years/>

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**MMR and Autism**  
**Andrew Wakefield Controversy**

- Andrew Wakefield
  - Pediatric gastroenterologist
  - Royal Free Medical School in London
- Published in Lancet a new disease
  - Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. **Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children.** *Lancet*. 1998 Feb 28;351(9103):637-41.  
**Retracted**

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**Features of Article**

- Introduced concept of Autistic enterocolitis
- 12 children included in the study
- On review
  - Original pathology results changed
  - Five had pre-existing conditions
  - Diagnosis of autism not present
    - Regressive autism in only one child
  - Time to symptoms after MMR was wrong
    - The review relied heavily on the temporal aspects for proof.
  - Eventually retracted, declared utterly false by editor
- Excellent journalistic work by Brian Deer

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**MMR and Autism**

- Additional Problems
  - Wakefield retained by lawyer who was suing vaccine manufacturers (unethical)
    - Study was funded for planned litigation
  - Conflict of interest because he patented a competing monovalent vaccine
    - Argued that giving multivalent vaccine caused disorder
  - He performed procedures that were not ethical such as ileocolonoscopies for no clinical benefit.

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## MMR and Autism

- Outcome
  - Wakefield was judged to be guilty of 30 charges
    - Dishonesty
    - Subjected children to invasive procedures that were not justified
    - Struck off the medical register
    - Described by GMC as dishonest, unethical, callous
  - Continues to maintain link between vaccines, autism
  - He began work at the Thoughtful House research center in Austin Texas in 2004
    - Resigned in 2010
  - He has spoken to preserve non-medical vaccine exemptions
  - Directed the anti-vaccination propaganda film Vaxxed: From Cover-up to catastrophe.

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## MMR and Autism

- Danish Study
  - 657,461 children
  - 6517 diagnosed with autism
  - Autism hazard ratio was 0.93 (0.85 - 1.02)
  - Subgroups were also looked at with no risk for autism
    - Sex, Date of birth, other vaccinations, siblings with autism, autism risk score
  - Risk factors for autism were: older mother, older father, poor APGAR score, low birthweight, preterm birth, large head, assisted birth and smoking during pregnancy

Hviid A, Hansen JV, Frisch M, Melbye M. Measles, Mumps, Rubella Vaccination and Autism: A Nationwide Cohort Study. Ann Intern Med. 2009;270:923-30.

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## Hannah Poling Controversy

- Daughter of Jon Poling, a neurologist and Terry, a lawyer.
- At 19 mo had five vaccines DTP, Hib, MMR, varicella, inactivated polio
- 2 days later became lethargic, irritable, febrile
  - Previously was interactive, playful and communicative
- 10 days later developed rash c/s vaccine induced varicella
- Months later noted to have neurologic and psychological delays, dx'd with encephalopathy and with autism d/o
  - Difficulties with language, communication, behavior
  - Dx'd also with mitochondrial enzyme d/o

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**Hannah Poling Controversy**

- Authored a case study with Andrew Zimmerman that speculated:
  - Young children who have dysfunctional cellular energy metabolism... might be more prone to undergo autistic regression between 18 and 30 months of age if they also have infections or immunizations at the same time.
- One co-author wrote – the etiology of mitochondrial dysfunction and how to define it in ASD is currently unclear – Further research is needed to better understand the role of mitochondrial dysfunction in the pathophysiology of ASD.

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**Hannah Poling Controversy**

- Law suit filed with DHHS under the Vaccine injury compensation program
- Requirements in this case are different than in a standard court of law.
- Require
  - Evidence of injury
  - Plausible argument, not scientific proof given by expert
    - Andrew Zimmerman - Pediatric Neurologist who studied ASD
    - Case report written by Poling and Zimmerman
- Conclusion: Plausible that vaccines aggravated a pre-existing condition that then manifested as autism-like symptoms
  - Compensation was awarded

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**Hannah Poling Controversy**

- Andrew Zimmerman submitted testimony of case of Cedillo v. Secretary of Health and Human Services.
- Opined that there was no evidence of an association between autism and alleged reaction to MMR and mercury.
- Later he told DOJ lawyers that he wanted to add a narrow and specific exception
  - Developmental regression may occur in children with underlying mitochondrial dysfunction and have a stress to their immune system or mitochondrial reserve.
  - Used as evidence by anti-vaxers of government cover up

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### Hannah Poling Controversy

- Several subsequent law suits brought before the VICP have not been compensated
- Both Poling and Zimmerman advocate all vaccinations

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### Thimerosal Hypothesis

- Used as a preservative in multiuse vials
- Contains ethylmercury, not methylmercury
- Children develop autism at the same time vaccines are given
- Never used in the MMR vaccine
- No longer added to most vaccines
  - Removed in 1999
  - Exceptions are Influenza, DTaP and DTaP-Hib
- Rates of autism have gone up with the removal of thimerosal from vaccines

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### Concern for the Quantity of Vaccines

- Vaccines contain only a small fraction of the antigens that babies are exposed to in the environment
  - Typically they are exposed to 2,000-6,000
  - Have capacity to respond to 100,000 at one time
  - Strep throat exposes one to 25-50 antigens
    - Comparable to the number with DTaP, IPV, HepB, Hib and rotavirus
- Number of antigen is much lower than previously
  - In 1980, the vaccines had 15,096 antigens
  - Currently they contain 173 antigens
    - Protein purification, rDNA technology

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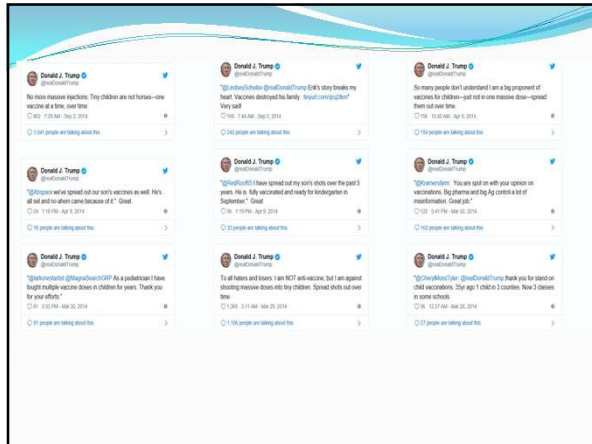
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## Web Resources

- Autism Speaks – [www.autismspeaks.org](http://www.autismspeaks.org)
- Autism Speaks – Colorado – [www.autismspeaks.org/site-wide/colorado](http://www.autismspeaks.org/site-wide/colorado)
- Autism Society of Colorado – <http://autismcolorado.info>
- Autism Society of America – [www.autism-society.org](http://www.autism-society.org)

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## Autism Resources

- CDC
- Autism Society of America
- Autism Speaks
- Autism Spectrum Disorders Video Glossary
- First Signs
- National Autistic Society (UK)
- Federation for Children with Special Needs
- Asperger's Association of New England
- Supplemental Security Income
- Autism Screening Tool Kit for Primary Care Providers
- Parent information: Autism spectrum disorders (Beyond the Basics)

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Thank You for Your Attention

Questions?

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