Integrating Treatment for Autism Spectrum Disorders Through the Life Cycle

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ACCME ACCREDITED

Idaho Autism Summit
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UCSF
University of California
San Francisco

Faculty Disclosure

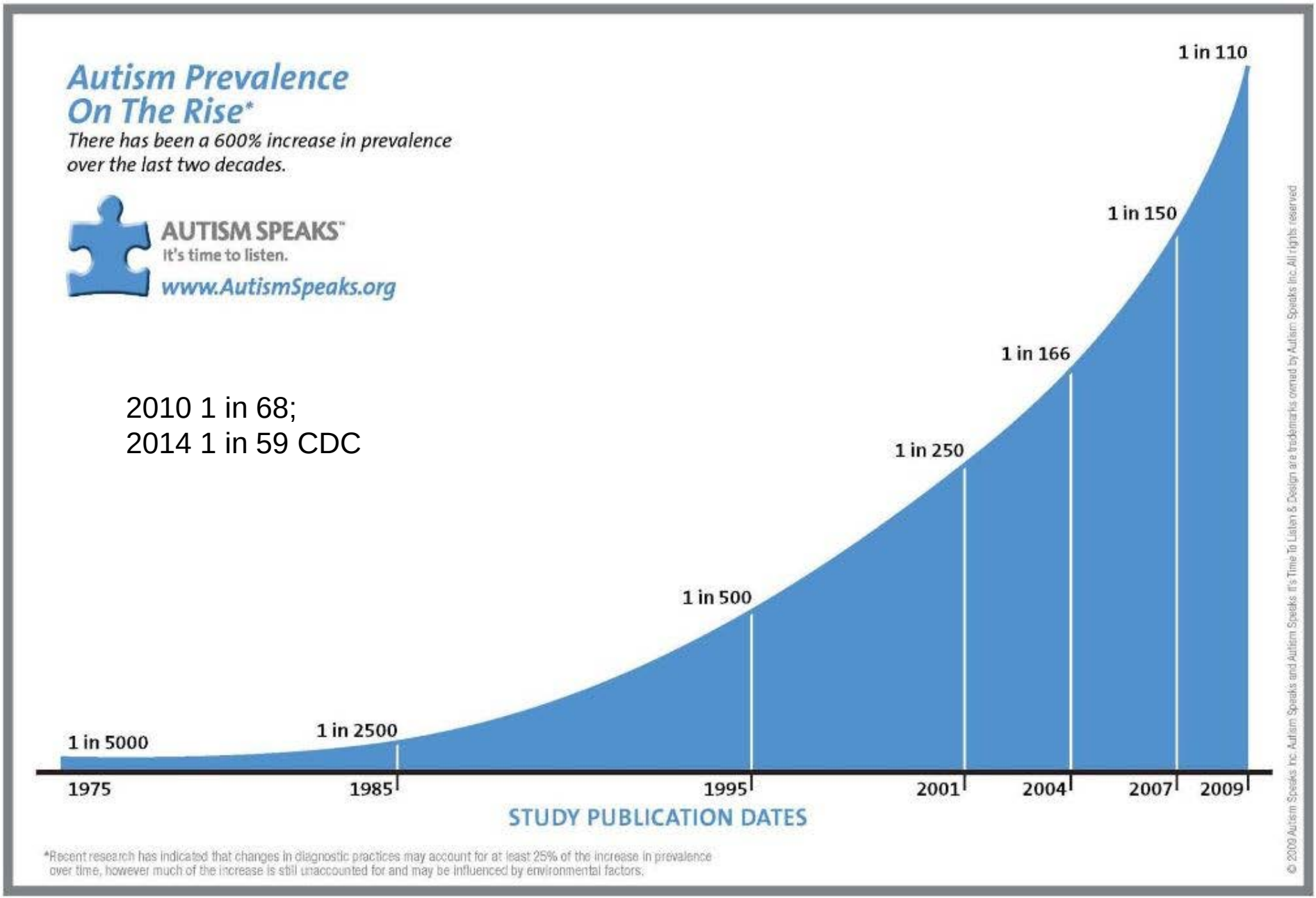
- Grants — Curemark, Roche, Otsuka
- Advisory Board — Curemark, BioMarin, Janssen, Axial Biotherapeutics
- Honoraria/Royalties: Oxford University Press, Taylor & Francis
- Dr. Hendren does intend to discuss the use of off-label/unapproved use of drugs

Learning Objectives

- Identify successes and challenges in the developmental progression through the life cycle for people with developmental disabilities and their families

- Identify and effectively treat comorbid medical, emotional and behavioral symptoms associated with autism spectrum disorders (ASD)

- Consider integrating biomedical treatments for ASD including conventional psychotropic medication and what has been referred to as CAM/CIM into a comprehensive program.



2010 1 in 68;
2014 1 in 59 CDC

Prevalence of Autism

- Possible explanations include
  - Diagnostic expansion and substitution
  - Better reporting
  - Increased recognition
  - Increasing acceptability
  - Immigration for services
  - Environmental toxins
  - Infectious and immune vulnerability
  - Epigenetic processes

Rutter M. *Acta Pediatr*. 2005;94(1):2-15. Centers for Disease Control and Prevention. Autism Spectrum Disorders. www.cdc.gov/ncbddd/autism. Accessed June 16, 2015. Hagerman R, Hendren RL (Eds). *Treatment of Neurodevelopmental Disorders: Targeting Neurobiological Mechanisms*. Oxford University Press; 2014.

ASD Genetic Etiology (Levels 1 & 2)

- Multiple genes: NRXN12q, 7q11.23, 15q11-13, 16p11.2, SHANK 3, 2, NLGN4, MTHFR 677>T, SEMA5A, 2Q22.1, GRIN2B, 5P14.1, CDH9, 10, FRX, PTEN
- Identical twins: 60% to 90%
  - Fraternal twins: 0% to 36%
  - Siblings: 4% to 19%
- Clear genetic etiology accounts for 25% of autism cases
- Hundreds of genetic mutations, some de novo, lead to many ways to develop and treat autism
- Is Precision Medicine Possible? Weiss KM, Issues Science and Technology in 2017

Levy D, et al. *Neuron*. 2011;70(5):886-897. Miles JH. *Genet Med*. 2011;13(4):278-294. Lossifov I, et al. *Neuron*. 2012;74(2):285-299. Murdoch JD, et al. *Curr Opin Genet Dev*. 2013;23(3):310-315.

ASD and Environmental Risk

- Documented: prenatal or early postnatal exposure to viral infections (rubella), valproic acid, thalidomide (Level 1)
- Proposed: influence of mercury, lead, environmental toxins, vaccines, lack of vitamin D (Levels 3 & 4)
- Parental age (older paternal and maternal; differences) (Level 1)
- Maternal metabolic conditions (Level 2)
- Influenza or fever during pregnancy (Level 2)
- Environmental pollution (Level 2)

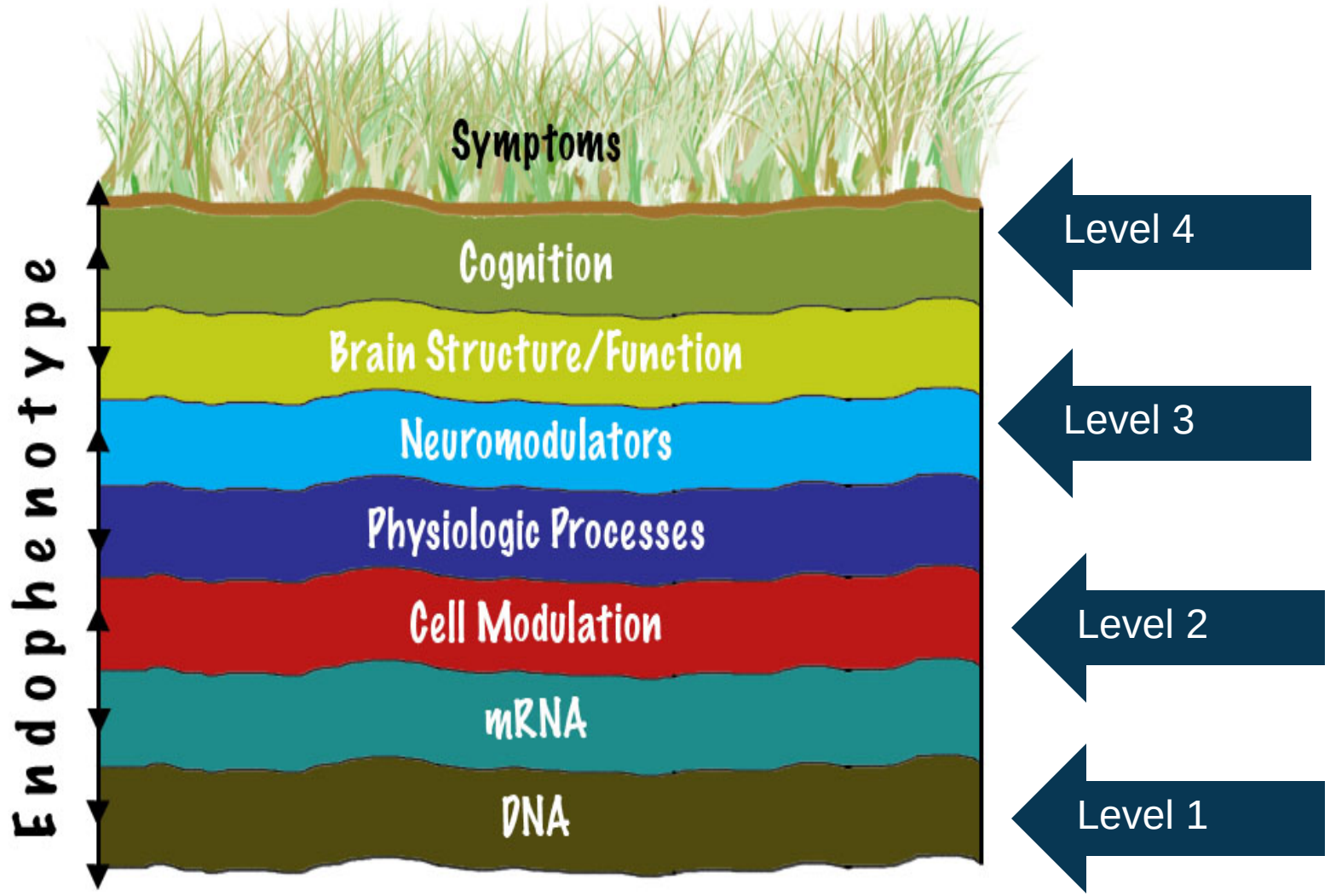
Herbert MR. *Curr Opin Neurol*. 2010;23(2):103-110. Landrigan PJ. *Curr Opin Pediatr*. 2010;22(2):219-225. Sandin S, et al. *Mol Psychiatry.* 2015;[Epub ahead of print]. Shelton JF, et al. *Autism Res*. 2010;3(1):30-39. Frans EM, et al. *JAMA Psychiatry*. 2013;70(5):516-521. Krakowiak P, et al. *Pediatrics*. 2012;129(5)e1121-e1128. Zerbo O, et al. *J Autism Dev Disord*. 2013;43(1):25-33. Schuler K, Institute for Agriculture and Trade Policy. www.iatp.org/files/2013_12_04_Autism_KS.pdf. Accessed June 16, 2015.

Model for Autism Etiology

- First hit – Genetic neurodevelopmental vulnerability
- Second hit – Environmental “stressor” and interaction between the two
- Third hit – Restricted development

Translating from “Terroir”: Model

Epigenetic Layer to Targeted Treatment



Hagerman R, Hendren RL (Eds). *Treatment of Neurodevelopmental Disorders: Targeting Neurobiological Mechanisms*. Oxford University Press; 2014.

Gene-Environment Interactions and Epigenetic Processes

(*Level 2*)

Goines P, et al. *Curr Opin Neurol*. 2010;23(2):111-117. James SJ, et al. *Am J Clin Nutr*. 2009;89(1):425-430. Frye RE, et al. *Pediatr Res*. 2011;69(5 Pt 2):41R-47R. Manji H, et al. *Nat Rev Neurosci*. 2012;13(5):293-307. Bell JG, et al. *Br J Nutr*. 2010;103(8):1160-1167. Rubenstein JL. *Curr Opin Neurol*. 2010;23(2):118-123. Harony H, et al. *Neurosignals*. 2010;18(2):82-97. Cunningham CL. *J Neurosci*. 2013;33(10):4216-4233.

Autism Through the Life Cycle

Brain Growth and Development

- Parental history and early developmental experiences also exert effects through epigenetic information not contained in the DNA sequence, which cause changes in gene expression
  - methylation and chromatin patterning
  - Histone acetylation
  - noncoding RNAs and mitochondria

- Transgenerational epigenetic effects interact with conditions at conception to program the developmental trajectory of the embryo and fetus, ultimately affecting the lifetime health of the child

Wells et al, 2016; Lane M, et al. *Science*. 2014;345(6198):756-760.

Brain Growth and Development

- We searched the MEDLINE database for studies published between January 1, 2005 and July 1, 2018 for perinatal risk factors and autism, risk factors such as infections, medications, and environmental factors including non-chemical stressors, chemical and nutritional factors. Then, we searched for interventions that may improve neurodevelopmental outcome including nutritional supplements during pregnancy, breastfeeding, and postpartum stress reduction.

- Our review, in agreement with other reviews, supports the possibility that interventions to normalize or mitigate these processes, particularly in the preconception or perinatal period, could lead to resilience and health in the developing and newborn child.

Cheng…Hendren, Medical Hypothesis, 127 (2019) 26-33

Hertz-Picciotto et al, 2018, Wang et al, 2017, Getahun et al., 2017, Hisle-Gorman et al., 2018

Pregnancy Autism Risk (Grade B Mod)

- Maternal Infection and Inflammation (congenital rubella)
- Environmental Toxicants (methylmercury, PCBs, Toluene, Arsenic)
- Air Pollution
- Pesticides
- Bisphenols and Phthalates
- Valproic Acid
- Thalidomide
- SSRIs
- Acetaminophen
- Heavy Metals

Atladottir et al., 2010; Ornoy et al, 2016; Muzhe & Chou, 2017; Eskenazi et al, 2008; Kondolot et al, 2016; Christensen et al. 2013; Croen et al, 2011; Bourkhris et al, 2016; Avella-Garcia CB et al, 2016; Kern 2016

Can Autism be Prevented? (Grade C Mod)

- Folic Acid and multivitamin Supplements before and during pregnancy associated with reduced risk of ASD (45,300 children; P<.001)
- Omega-3 Polyunsaturated Fatty Acid
- Vitamin D
- Antioxidants
- Iron
- Choline/phosphatidylcholine
- One practice minimized toxicant exposure; maximized breastfeeding; probiotics, nutritional counseling; limited antibiotics; minimized acetaminophen
  - Out of 294 general pediatric patients followed since 2005 there were 0 new cases of autism

Levine SZ et al., 2018; Suren et al., 2013; Morgese & Trabace, 2016; Stubbs et al., 2016; Zhang et al, 2015; Schmidt et al., 2014; Ross et al, 2016; Mumper E. *North American Journal of Medicine and Science*. 2013;6(3):134-144

P2i – Preconception to Infancy

- Goal is to establish a program that reduces miscarriages and helps ensure infants a healthy start in life
- www.ForumP2i.com
- University of Georgia Center for Excellence
- Be Fruitful: The Essential Guide to Maximizing Fertility and Giving Birth to a Healthy Child, Victoria Maizes, MD, Scribner, NY, 2013

Early Intervention

The majority of research and clinical programs are targeted at younger children where neurodevelopmental processes are more plastic

Parental Concerns, Provider Response, and Timeliness of ASD Dx

- Compared with children with ID/DD, children with ASD were younger when parents first had concerns and first discussed those concerns with a provider
- Compared with parents of children with ID/DD, parents of children with ASD were less likely to receive proactive responses to their concerns and more likely to receive reassuring/passive responses
- Among children with ASD, those with more proactive provider responses to concerns had shorter delays in ASD diagnosis compared with those with passive/reassuring provider responses
- Although parents of children with ASD have early concerns, delays in diagnosis are common, particularly when providers' responses are reassuring or passive, highlighting the need for targeted improvements in primary care

ID/DD = intellectual disorder/developmental disorder.

Zuckerman KE, et al. *J Pediatr*. 2015;166(6):1431-1439.e1.

Later Intervention

Is late adolescence and young adulthood too late to intervene?

Development in ASD in Adolescence (Levels 2 & 3)

- Microstructure of the thalamus, a key sensory and motor brain area, appears to develop differently in individuals with autism spectrum disorder with differences narrowing with age.

- PEERS social skills treatment improves particular aspects of emotional, behavioral, and social functioning that may be necessary for developing and maintaining quality peer relationships and remediating social isolation in adolescents with ASD.

Ecker C, et al. *Lancet Neurol*. 2015;S1474-4422(15)00050-2. Lainhart JE. *Curr Opin Psychiatry*. 2015;28(2):76-82. McLaughlin K et al, Autism Res. 2017; N Lordo D, J Autism Dev Disord. 2017 47(1):203-214.

Postsecondary Employment Experiences among Young Adults with ASD

- Approximately **one-half (53.4%) of young adults with ASD had ever worked for pay** outside the home since leaving high school, the lowest rate among disability groups

- Young adults with an ASD **earned an average of $8.10/hour**, significantly lower than average wages for young adults in the comparison groups, and held jobs that clustered within fewer occupational types. Odds of ever having had a paid job were higher for those who were older, from higher-income households, and with better conversational abilities or functional skills

Roux AM, et al. *J Am Acad Child Adolesc Psychiatry*. 2013;52(9):931-939.

Primary Care for Adults with ASD

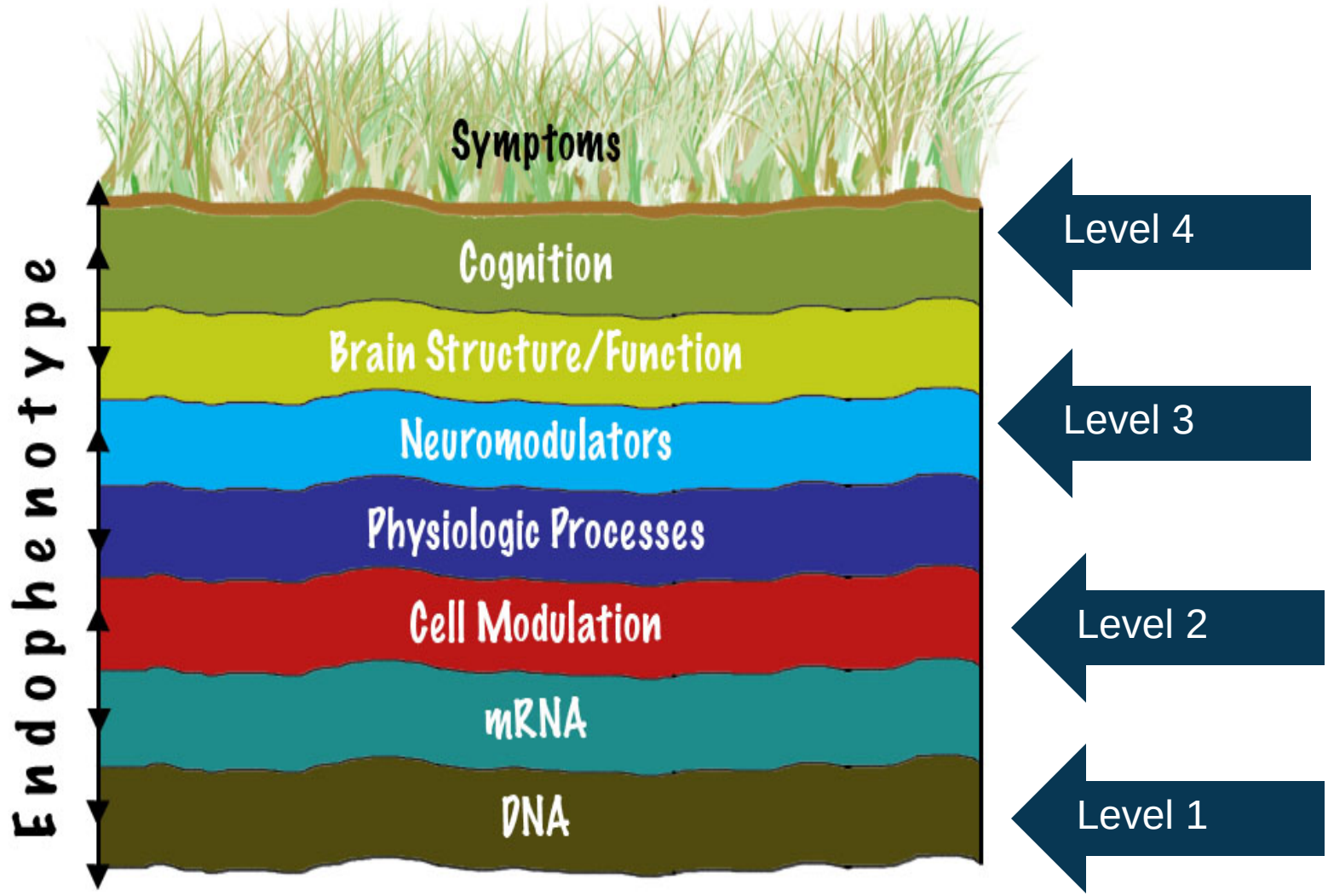
- Individuals' **challenges fall along spectra on multiple axes** (spoken language, written communication, performance on daily living activities, need for consistency, sensory sensitivity, emotional regulation)
- Adults with ASD have **increased rates of chronic medical illness**, including epilepsy, GI disorders, feeding and nutritional problems, metabolic syndrome, anxiety, depression, and sleep disturbances
- Youth age 11 to 22 years with ASD and ID were reported to **thrive less than peers** with ID only
- Group differences in **sociocommunicative ability and school participation** mediated the relationship between ASD and less thriving

GI = gastrointestinal. Nicolaidis C, et al. *Med Clin North Am*. 2014;98(5):1169-1191. Weiss JA, et al. *J Autism Dev Disord*. 2015;[Epub ahead of print].

Autism Comorbidity & Interventions

Translating from “Terroir”: Model

Epigenetic Layer to Targeted Treatment



Hagerman R, Hendren RL (Eds). *Treatment of Neurodevelopmental Disorders: Targeting Neurobiological Mechanisms*. Oxford University Press; 2014.

Level-Based Interventions

Level 4 – Behavioral interventions, family support, structure

Level 3-4 – Speech and language, OT, therapy, CBT

Level 2-3 – Pharmacotherapy

Level 2 – Biomedical/epigenetic

Level 1 – Gene modification

CBT = cognitive-behavioral therapy; OT = occupational therapy.

Behavioral Treatments for ASD (Level 4)

- ABA – Discrete Trials Training (Level 1)
- TEACCH (Level 3)
- Pivotal Response Training (Level 1)
- Incidental Teaching Approach (Level 2)
- Floor time & Developmental, Individual-Difference Relationship-Based model (Level 3)
- Early Start Denver Model (Level 1)
- Naturalistic Developmental Behavioral Interventions (NDBI) for ASD (Level 2)

ABA = Applied Behavioral Analysis; TEACCH = Treatment, Education of Autistic & Communication Handicapped Children. Koegel RL, et al. *J Clin Child Psychol*. 2001;30(1):19-32. Greenspan S, et al. *Engaging Autism*. Cambridge, MA: Da Capo Press; 2006. Wallace KS, et al. *J Child Psychol Psychiatry*. 2010;51(12):1300-1320. Tachibana Y, PLoS One. 2017, NDBI for ASD, Bruinsama, Y, 2019

ASD Medical Comorbidities

- Sleep Disorders (50% - 80%)
  - symptom severity,
  - comorbidity
- GI abnormalities (30%–70%)
  - Correlation with symptom severity
  - 85-95% of 5-HT receptors in gut
- Epilepsy (30%)
  - two waves;
  - 2 x higher mortality;
  - Likely worsens prognosis

Tye et al, Frontiers in Psychiatry, 2019; 23:9:751; Werner E, et al. *Arch Gen Psychiatry*. 2005;62(8):889-895. Buie T, et al. *Pediatrics*. 2010;125 Suppl 1:S1-S18. Tharp B. In: Ozonoff S, et al (Eds). *Autism Spectrum Disorders: A Research Review for Practitioners*. Arlington, VA: American Psychiatric Publishing, Inc; 2003. Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Textbook Revision).* Arlington, VA: American Psychiatric Association; 2000. McDougle CJ, et al. *J Clin Psychiatry*. 2005;66 Suppl:9-18. Frye RE, et al. *Pediatr Res*. 2011;69(5 Pt 2):41R-47R. Kohane IS, et al. *PloS One*. 2012;7(4):e 33224.

ASD Medical Comorbidities

- Immune Disorders
  - Food allergies, allergic rhinitis, atopic dermatitis, autoimmune disorders, asthma
  - Increased proinflammatory cytokines
  - Corticosteroids, celecoxib, IVIG

- Higher than expected rates of other medical conditions – eczema, allergies, asthma, ear and respiratory infections, headache

Tye et al, Frontiers in Psychiatry, 2019; 23:9:751; Werner E, et al. *Arch Gen Psychiatry*. 2005;62(8):889-895. Buie T, et al. *Pediatrics*. 2010;125 Suppl 1:S1-S18. Tharp B. In: Ozonoff S, et al (Eds). *Autism Spectrum Disorders: A Research Review for Practitioners*. Arlington, VA: American Psychiatric Publishing, Inc; 2003. Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Textbook Revision).* Arlington, VA: American Psychiatric Association; 2000. McDougle CJ, et al. *J Clin Psychiatry*. 2005;66 Suppl:9-18. Frye RE, et al. *Pediatr Res*. 2011;69(5 Pt 2):41R-47R. Kohane IS, et al. *PloS One*. 2012;7(4):e 33224.

ASD Medical Comorbidities

- Mental retardation (70% of full syndrome)
- Regressive autism (20%–47%)
- Mitochondrial disorders

Tye et al, Frontiers in Psychiatry, 2019; 23:9:751; Werner E, et al. *Arch Gen Psychiatry*. 2005;62(8):889-895. Buie T, et al. *Pediatrics*. 2010;125 Suppl 1:S1-S18. Tharp B. In: Ozonoff S, et al (Eds). *Autism Spectrum Disorders: A Research Review for Practitioners*. Arlington, VA: American Psychiatric Publishing, Inc; 2003. Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Textbook Revision).* Arlington, VA: American Psychiatric Association; 2000. McDougle CJ, et al. *J Clin Psychiatry*. 2005;66 Suppl:9-18. Frye RE, et al. *Pediatr Res*. 2011;69(5 Pt 2):41R-47R. Kohane IS, et al. *PloS One*. 2012;7(4):e 33224.

ASD Differential Diagnosis or Comorbidity

- ADHD
- OCD
- Tics and Tourette's
- Overanxious Disorder
- Bipolar Disorder
- Depressive Disorder
- Learning Disorder

- Psychotic Disorder
- Catatonic Autism
- Aggression – 53% – younger; associated with medical comorbidities

Rosen TE, International Review of Psychiatry, (2018) 30(1) 40-61; Hendren RL. In: Ozonoff S, et al (Eds). *Autism Spectrum Disorders: A Research Review for Practitioners*. Arlington, VA: American Psychiatric Publishing, Inc; 2003. Mazurek MO, et al. *Res Autism Spectr Disord*. 2013;7(3):455-465.

Summary of Conventional Medications for Autism (Level 2)

- Stimulants: works for some; start low and go slow
- Antidepressants: maybe for anxiety; OCD and ASD mixed
- Alpha-adrenergic agonists: worth a try for anxiety but limited studies
- Anticonvulsants: ? mood dysregulation + neurologic abnormalities; limited studies
- Antipsychotics: indication for risperidone and aripiprazole (Level 1), but adverse effects. ? asenapine, negative lurasidone study in children

Risperidone and aripiprazole (irritability) are the only FDA-approved medications or biomedical agents for treating autism.

Handen BL, et al. *Int J Adolesc Med Health*. 2011;23(3):167-173. Anagnostou E, et al. *Curr Opin Pediatr*. 2011;23(6):621-627. Correll CU, et al. *J Clin Psychiatry*. 2011;72(5):655-670. Kaplan G, et al. *Pediatr Clin North Am*. 2012;59(1):175-187.

Medications to Consider (Level 3 & 4)

- Propranolol
- Naltrexone
- Buspirone
- Memantine
- Amitriptyline

Narayanan A, et al. *Brain Imaging Behav*. 2010;4(2):189-197. King BH, et al. *J Am Acad Child Adolesc Psychiatry*. 2001;40(6):658-665. Posey DJ. *Am J Psychiatry*. 2004;161(11):2115-2117. Chez MG, et al. *J Child Neurol*. 2004;19(3):165-169. Deutsch SI, et al. *Clin Neuropharmacol*. 2010;33(3):114-120. Brown N, et al. *Med Hypotheses*. 2009;72(3):333-337. Buitelaar JK, et al. *J Clin Psychiatry*. 1998;59(2):56-59. Ghaleiha A, et al. *Int J Neuropsychopharmacol*. 2013;16(4):783-789. Bhatti I, et al. *J Autism Dev Disord*. 2013;43(5):1017-1027.

Autism Pharmacologic Challenges

(Levels 2, 3, & 4)

- Sleep – melatonin, GABA/L-theanine, hydroxyzine, clonidine, trazodone, mirtazapine, olanzapine
- Skin picking – NAC, SSRIs, duloxetine, buspirone
- Screeching, yelping – divalproex
- Tx-resistant OCD – NAC, L-methylfolate, clomipramine + SSRI
- Anxiety – GABA-A, pregabalin

www.ClinicalTrials.gov
Based on my experience, other practitioners' experience, and reports from family members.

CAM/CIM/Biomedical and Autism

- National Center for Complementary and Alternative Medicine defines CAM as “a group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine”
- Up to 70% of people with ASD are reported to be using some form of biological treatment
- Up to 28% to 82% of children recently diagnosed with autism use CAM
- The main reasons for choosing CAM were related to concerns with the safety and adverse effects of prescribed medications
- Physicians not perceived as a knowledgeable resource

Birdee GS, et al. *Pediatrics*. 2010;125(2):249-256. Wong HH, et al. *J Autism Dev Disord*. 2006;36(7):901-909. Perrin JM, et al. *Pediatrics*. 2012;130 Suppl 2:S77-S82. Huang A, et al. *J Altern Complement Med*. 2013;19(9):746-750. Hanson E, et al. *J Autism Dev Disord*. 2007;37(4):628-636.

Gene-Environment Interactions and Endophenotype (Terroir Level 2; Evidence Levels 2 & 3)

- Immune abnormalities/inflammation
- Oxidative stress
- Disturbed methylation
- Mitochondrial dysfunction
- Free fatty acid metabolism
- Excitatory/inhibitory imbalance
- Hormonal effects
- Microglia

Goines P, et al. *Curr Opin Neurol*. 2010;23(2):111-117. James SJ, et al. *Am J Clin Nutr*. 2009;89(1):425-430. Frye RE, et al. *Pediatr Res*. 2011;69(5 Pt 2):41R-47R. Manji H, et al. *Nat Rev Neurosci*. 2012;13(5):293-307. Bell JG, et al. *Br J Nutr*. 2010;103(8):1160-1167. Rubenstein JL. *Curr Opin Neurol*. 2010;23(2):118-123. Harony H, et al. *Neurosignals*. 2010;18(2):82-97. Cunningham CL. *J Neurosci*. 2013;33(10):4216-4233.

A New Paradigm (Levels 3 & 4)

- Significant subsets of people with autism have intestinal inflammation, digestive enzyme abnormalities, metabolic impairments, oxidative stress, mitochondrial dysfunction, and immune problems that range from immune deficiency to hypersensitivity to autoimmunity
- In many cases, improvement of autistic symptoms is achieved by a combination of nutritional recommendations, prescription medications, and addressing the underlying medical conditions seen in these individuals

Mumper E. *North American Journal of Medicine and Science*. 2012;5(3):180-184.

BioMedical/CIM Treatments

- Melatonin
- Omega-3
- Vitamin D3
- Methyl B12
- NAC
- Vitamin/Mineral Supplements
- Diet
- Microbiome
- Pancreatic Digestive Enzymes
- Balovaptin
- CBD/THC

PRONTO Lab

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Kevin Delucchi, Ph.D.
Statistician

Jessica Wahlberg
Clinical Research Coordinator

Crystal Chen
Research Data Analyst

The Oak Hill School

Oak Hill serves a heterogeneous population of children, adolescents, and young adults, all of whom have autism spectrum disorder (ASD) or other neurologically-based disorders of relating and communicating. Students receive special education instruction and customized on-site clinical programs which may include speech/language pathology, occupational therapy, and group and individual psychotherapy. A portion of students have received recent functional behavior analyses (FBAs), with school staff implementing positive behavior intervention programs. The school also offers arts-based therapies and adaptive arts instruction.

Dang, K., Bent, S., Lawton, B., Warren, T., Widjaja, F., McDonald, M. G., Breard, M., O'Keefe, W., Hendren, R. L. (2017) Integrating autism care through a school-based intervention model: A pilot study. *Journal of Clinical Medicine.* doi:10.3390/jcm6100097.

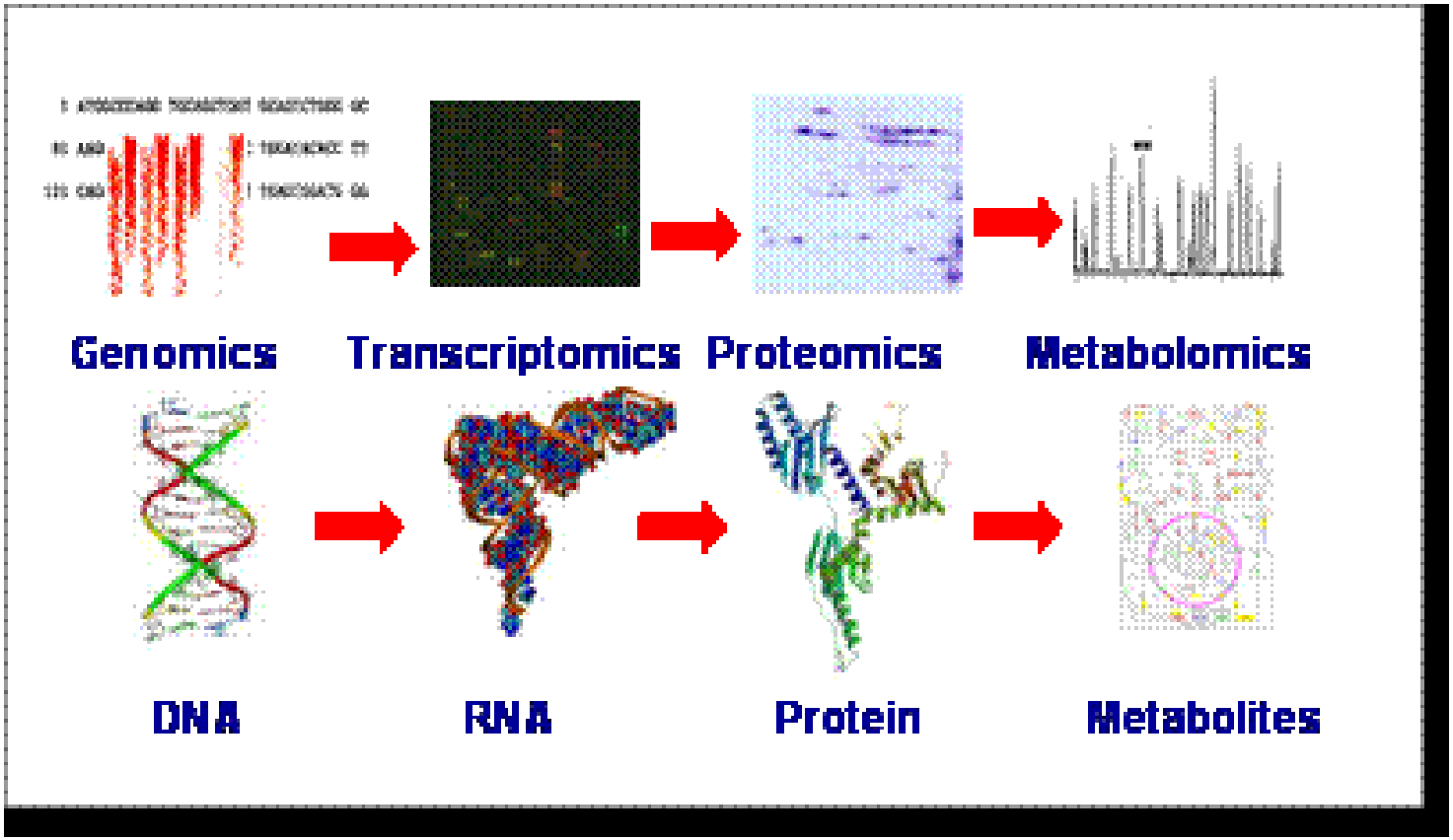
UCSF & OAK HILL SCHOOL

INTEGRATING MEDICINE AND EDUCATION

Optimize children's internal environment to best utilize educational, social, and life skills interventions by:

- Identifying educational and treatment targets
- Measuring effects of interventions
  - behavioral, academic, social, physiological
- Creating a Medical Home
- Enhancing biomedical resilience
- Developing new effective treatments

Supported by J. S. Foundation


Genomics
Transcriptomics
Proteomics
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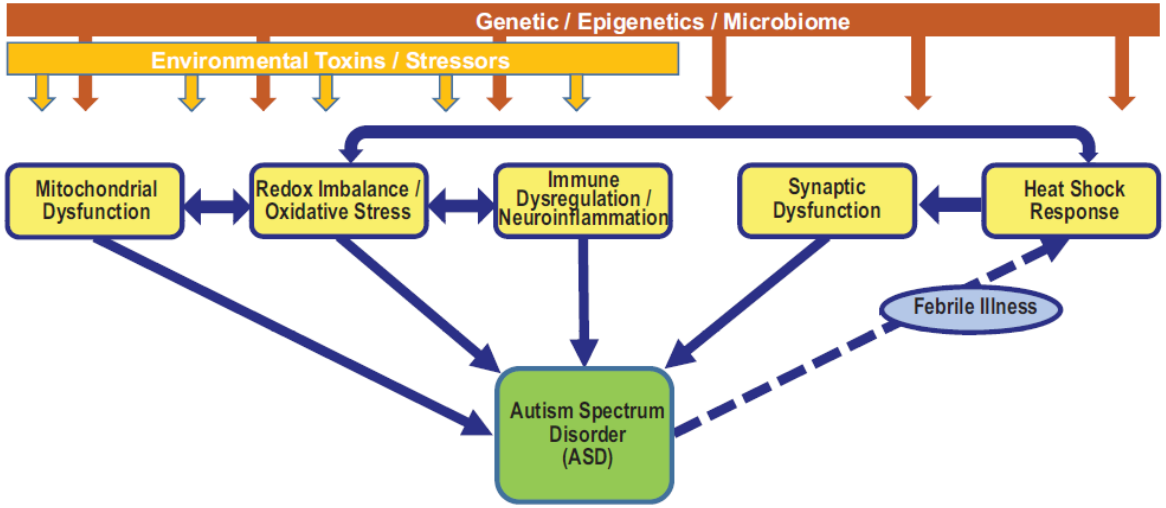
DNA
RNA
Protein
Metabolites

ASD



- ASD is associated with many cellular and biochemical abnormalities:

  - Increased oxidative stress
  - Lower capacity for cells to deal with oxidative stress (including decreased antioxidant glutathione)
  - Mitochondrial dysfunction
  - Neuro*inflammation*

- Sulforaphane has been shown to positively assist with all of these

Liu, Talalay, Fahey: Biomarker-Guided Strategy for Treatment of Autism Spectrum Disorder (ASD), CNS & Neurological Disorders - Drug Targets, 2016, Vol. 15, No. 5

Sulforaphane Trial at Oak Hill School

Methods

- 15 subjects, ages 5-22 (mean age 14.7), with ASD diagnoses, attending Oak Hill School (San Anselmo, CA)
- Open-label, 12-week study
- Daily, weight-based dose of sulforaphane
- Baseline and final ABC, SRS, and urine sample

Results

- ABC improved -7.1 points (95% CI: -17.4 to 3.2).
- SRS improved significantly -9.7 points (95% CI: -18.7 to -0.8).
- 77 urinary metabolites were correlated with changes in symptoms, clustered into the following pathways:
  - Oxidative stress
  - Amino acid/gut microbiome
  - Neurotransmitters
  - Hormones
  - Sphingomyelin metabolism

Bent …Hendren, Molecular Autism, 2018

Other trials at OHS and Goals

Recently Completed/Upcoming clinical trials

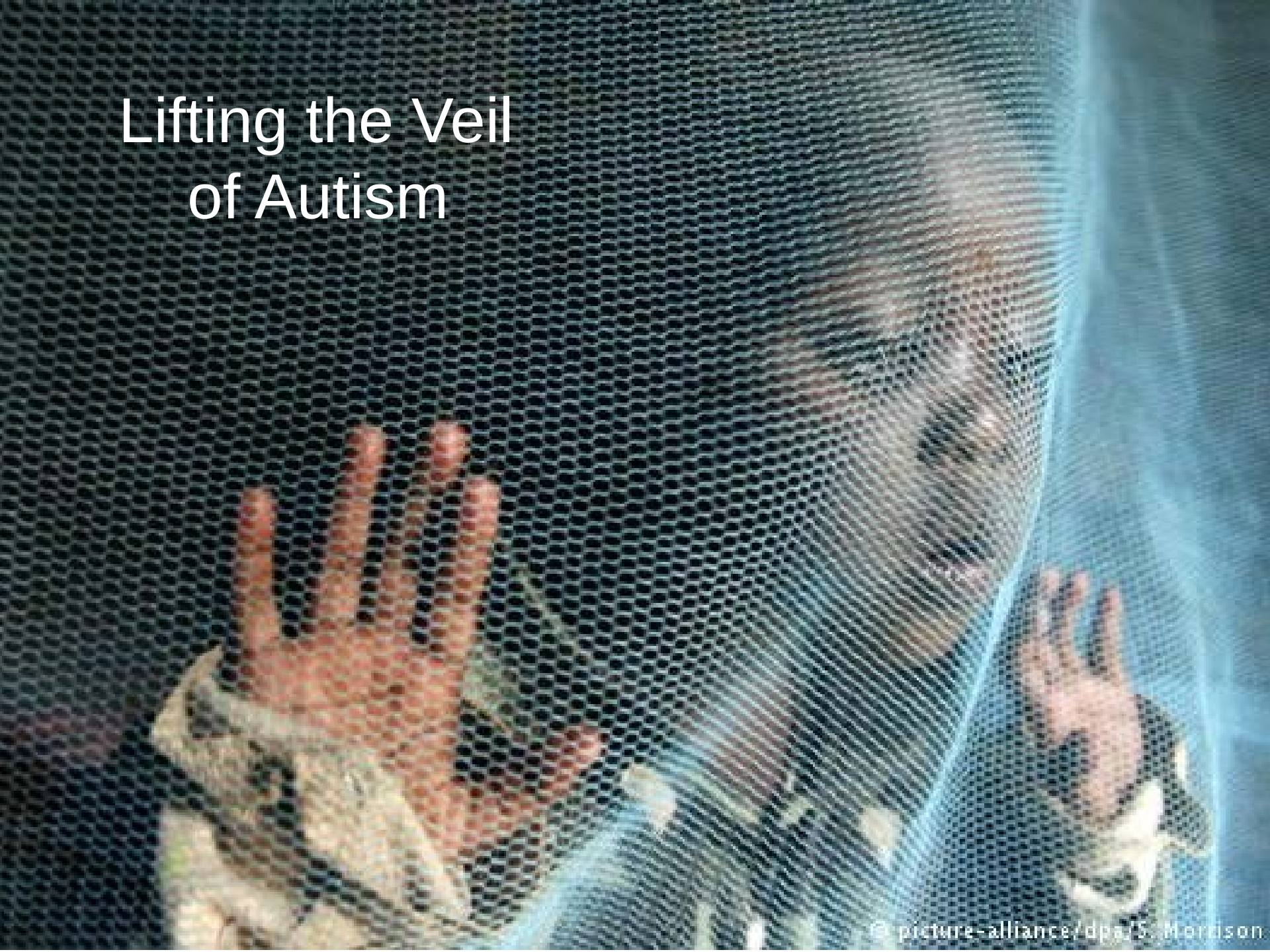
- Folinic acid
  - Decreased folate levels implicated in autism and other developmental differences
  - Planned 3-month trial at Oak Hill with urinary metabolomics
  - Small trial and trend toward improvement
- CM-AT
  - Pancreatic digestive enzyme to increase levels of chymotrypsin in the body, donated by Curemark, LLC.
  - Decreased chymotrypsin levels implicated in autism
  - Planned 3-month trial at Oak Hill with urinary metabolomics
  - Pending IND approval from FDA

Other directions

- PEERS
- UCSF Clinic at OHS
- OMT study

Eventual goals

- Develop metabolomic methods to identify and create individualized, targeted, biomedical treatment plans
- Develop integrated care program between parents, teachers, and clinicians
  - Dang et al. (2017)


Lifting the Veil
of Autism
© picture-alliance/dpa/S. Morrison

Integrated Approach to Autism Treatment

- Medical – genetic, neurology, GI, other medical symptoms
- Ancillary – speech, OT
- Behavioral
- Treat associated symptoms – pharmacology
- Biomedical assessment and treatments – melatonin, omega-3, vitamin D3, probiotics, digestive enzymes
- **Building personal relationships and resilience are all encompassing**

Practical Take-Aways

1. New research in classification and gene by environment interaction are changing the way we conceptualize ASDs
2. Biomedical assessment and treatments are changing our practices to a more “whole body” “integrated” treatment focused on treatment targets and building resilience
3. Several biomedical treatments have adequate evidence to use for many patients including melatonin, probiotics, omega-3s, and possibly vitamin D3, sulforaphane, folinic acid, methyl B12, restrictive diets, vitamins and digestive enzymes.
4. In my practice, I suggest Omega-3, vitamin D, multiple vitamin and if indicated melatonin and NAC to all patients. I discuss trying sulforaphane, folinic acid, probiotics, digestive enzymes, and CoQ10.


July 4 2000

Psychopharm & CIM Appendix

ADHD and ASD

- Clinically significant symptoms of ADHD have been reported in 16% to 66% of children with ASD
- Greater impairment in adaptive functioning and poorer health-related quality of life in children with ASD and ADHD than when there are fewer ADHD symptoms
- Allowed as a comorbidity in *DSM-5*

Hanson E, et al. *J Autism Dev Disord*. 2013;43(6):1459-1464. Sikora DM, et al. *Pediatrics*. 2012;130 Suppl 2:S91-S97.

ASD and ADHD cont

- ASD and ADHD have shared genetic heritability and are both associated with shared impairments in social functioning and executive functioning.

- For children diagnosed with ADHD (n=48) or ASD (n=164), of the ADHD sample, 21% met the ASD cut-offs on the ADOS and 30% met ASD cut-offs on all domains of the ADI-R. Four social communication ADOS items (Quality of Social Overtures, Unusual Eye Contact, Facial Expressions Directed to Examiner, and Amount of Reciprocal Social Communication) adequately differentiated the groups.

Antshel KM: Curr Psychiatry Rep, (2019) 22:21(5):34; Grzadzinski R; Mol Autism (2016) 19;7:7

Stimulants and ASD

- Evidence for effectiveness mixed with less information for amphetamines
- Early studies suggest ineffectiveness and poor tolerability
- RUPP – RCT of 72 youth using methylphenidate suggest improvement in some, but with lower rates of improvement and more adverse events than in children with ADHD without ASD
- Atomoxetine – small studies suggest improvement, but less than children with ADHD without ASD
  - ATX + Parent Training for ASD + ADHD – better side effect profile

RUPP = Research Units on Pediatric Psychopharmacology

Campbell M. *Biol Psychiatry*. 1975;10(4):399-423. Research Units on Pediatric Psychopharmacology Autism Network. *Arch Gen Psychiatry*. 2005;62(11):1266-1274. Arnold LE, et al. *J Am Acad Child Adolesc Psychiatry*. 2006;45(10):1196-1205.; Handen et al., JAACAP 2015
Politte LC et al, Harv Rev Psychiatry. 2014 22(2):76-92.

Alpha-2 Adrenergic Agonists

- Clonidine – 2 DBPC trials
  - Modest benefit for overactivity, sensory responses, decreased irritability, stereotypy, and oppositional behavior
  - Sedation, fatigue, decreased activity
- Guanfacine
  - retrospective (N = 80), prospective (N = 11)
    - Decreased hyperactivity
    - Sedation, constipation, sleep disruption, irritability
  - Multisite RCT (N=62) ER for 8 weeks; modal dose 3mg
    - 43.6% decline in ABC- Hyperactivity active vs 13.2% placebo
    - CGI-I 50% vs 9.4%

Jaselskis CA, et al. *J Clin Psychopharmacol*. 1992;12(5):322-327. Fankhauser MP, et al. *J Clin Psychiatry*. 1992;53(3):77-82. Posey DJ, et al. *J Child Adolesc Psychopharmacol*. 2004;14(2):233-241. Handen BL, et al. *J Dev Behav Pediatr*. 2008;29(4):303-308; Scahill et al, AM J Psychiatry 2015

ASD and ADHD cont

- Cochrane review of methylphenidate for ASD found short term use of methylphenidate might improve symptoms of hyperactivity and possibly inattention with no evidence of negative impact on core symptoms of ASD or that it improves social interaction, stereotypical behaviors or overall ASD.

- Case control study of 347 children found ADHD symptoms predict poorer adaptive behavior for autistic children across settings, even for children with subclinical co-occurring ADHD symptoms

Sturman N Corchrane Database Syst Rev (2017) 11:CD011144Yerys BE (2019) JAACAP, 58(5):525-533

Restricted Repetitive Behaviors and Inhibitory Control in ASD across the Lifespan

- Having a comorbid diagnosis of ID was also associated with repetitive behaviors, with individuals diagnosed with ID exhibiting more repetitive behaviors than individuals with ASD only
- Age-related pattern of symptom abatement in Restricted Repetitive Behavior is not dependent upon gender, a comorbid diagnosis of ID, or taking psychotropic medication
- However, brain processes underlying inhibitory control appear to be underdeveloped in ASD and develop differently from adolescence to adulthood in ASD

Esbensen AJ, et al. *J Autism Dev Disord*. 2009;39(1):57-66. Padmanabhan A, et al. *Autism Res*. 2014;8(2):123-135.

Depressive Symptom Trajectories in ASD

- Prevalence of comorbid depression seems to correlate with higher functioning forms of ASD and increasing age.
- Internalizing symptoms were associated with poorer emotional regulation in school age, and with lower life satisfaction and greater social difficulties in early adulthood
- Although symptom levels in females increase at a faster rate throughout adolescence, males with ASD appear to have elevated levels of depressive symptoms in school age that are maintained into young adulthood

DeFilippis M, Children (Basel) (2018); 5(9); Gotham K, et al. *J Am Acad Child Adolesc Psychiatry*. 2015;54(5):369-376.

Suicide and ASD

- National survey of 185 people with ASD aged 14 to 80 found 49% in the clinical range for depression and 36% reporting recent suicidal ideation. Females reported higher depression rates than males. Loneliness and social support operate respectively as protective and risk factors for depression and suicidal ideation.

- Nationwide survey in Taiwan found patients with ASD had increased risk of suicide attempts compared to those without ASD especially in adolescents and young adults.

Hedley D, Depress Anxiety, (2018) 35 (7):648-657; Chen MH. J Clin Psychiatry (2017) 78(9)e1174-e1179

SSRIs and Autism

- Serotonin consistently shown to be dysregulated in ASD
- Fluvoxamine and sertraline demonstrate improvement in aggression and social relations
- Perhaps improved language and correlation with family history of affective disorder
- DBPC trial of fluoxetine in adults found significant improvement in repetitive behaviors
- "Lack of Efficacy of Citalopram for Repetitive Behaviors in ASD" DBPC trial with 149 children (5 to 17 years) with ASD, mean dose 16.5 mg/day) No significant difference on CGI-I or CYBOCS

Cook EH Jr, et al. *Mol Psychiatry*. 1997;2(3):247-250. McDougle CJ, et al. *Arch Gen Psychiatry*. 1996;53(11):1001-1008. DeLong GR, et al. *Dev Med Child Neurol*. 2002;44(10):652-659. Hollander E, et al. *Neuropsychopharmacology*. 2005;30(3):582-589. Posey DJ, et al. *J Child Adolesc Psychopharmacol*. 2006;16(1-2):181-186. King BH et al. Arch Gen Psychiatry. 2009;66:583-590.

Psychotic Disorder and Bipolar Disorder in ASD

- 9062 people with ASD in Sweden followed from age 17 to 27 years
- AORs for nonaffective psychotic disorder and bipolar disorder in people with non-ID ASD were 12.3 (95% CI, 9.5-15.9) and 8.5 (95% CI, 6.5-11.2), respectively, which was greater than ID ASD
- This rate is higher than in age and sex matched individuals without ASD in the general population
- May have to do with common underlying genetic risk factors or to exposure sensitivity

AOR = adjusted odds ratio.

Selten JP, et al. *JAMA Psychiatry*. 2015;72(5):483-489.

Disruptive Mood Dysregulation Syndrome (DMDD)

- Severe temper outbursts at least three times a week
- Sad, irritable or angry mood almost every day
- Reaction is bigger than expected
- Child must be at least six years old
- Symptoms begin before age ten
- Symptoms are present for at least a year
- Child has trouble functioning in more than one place (e.g., home, school and/or with friends)
- Stimulants, antipsychotics, mood stabilizers

Antipsychotics and ASD

- A Double-Blind Placebo Controlled Trial of Risperidone in Autistic Disorder
  - 8 weeks of treatment associated with statistically significant decrease in self-injury, aggression, agitation, stereotypy and hyperactivity
- Aripiprazole in the Treatment of Irritability in Youth with Autism
  - 8 week DBPC fixed and flexible dose study of over 300 children & adolescents 6 to 17 yrs
  - 85% completion; Average dose 8.1mg; 50 – 52% responders based on ABC-I and CGI-I of much or very much improve

McCracken JT et al*. N Engl J Med*. 2002;347:314-321.*;* Marcus RN et al. *J Am Acad Child Adolesc Psychiatry*. 2009;48:1110-1119; Owen R et al. *Pediatrics*. 2009;124(6):1533-1540.; Politte LC et al, Harv Rev Psychiatry. 2014 22(2):76-92.

Autism Biomedical CIM Interventions

Melatonin

- Endogenous neurohormone causes drowsiness, establishes circadian rhythms and synchronization of peripheral oscillators, and is produced from serotonin
- Review and meta-analysis of 35 studies reported that of 18 treatment studies, there were 5 RCTs (N = 61, 2 to 10 mg/day) where sleep duration (44 min, ES = .93) was increased, sleep onset latency was decreased (39 min, ES = 1.28), but nighttime awakenings were unchanged
- Adverse effects were minimal to none
- May also benefit social communication impairments and stereotyped behaviors or interests

Tordjman S, et al. *Int J Mol Sci*. 2013;14(10):20508-20542. Rossignol DA, et al. *Dev Med Child Neurol*. 2011;53(9):783-792.

Vitamin D
Vitamin D Council

- “Ecological Evidence” – Northern latitudes, rainfall, skin pigment. Low levels of vitamin D reported
- Vitamin D activates serotonin-synthesizing gene
- Vitamin D is a “potent neurosteroid”
- UCSF study
  - 25(OH)D at or below 30 ng/mL
  - Initial loading dose of 10,000 IU of D3, then 300/IU/kg of vitamin D3
  - Target level 90 ng/mL
  - Safety measured by 25(OH)D and calcium level, tremor, weakness, fatigue, diarrhea, anorexia, headache confusion, psychosis

Jia et al. Pediatrics, 2014; Patrick RP, et al. *FASEB J*. 2014;28(6):2398-2413. McGrath J, et al. *Trends Neurosci*. 2001;24(10):570-572.

Methyl B12 Study
UCSF (Autism Speaks)

- 53 children between the ages of 3 and 7 years enrolled in study at UCSF funded by Autism Speaks
- Eligible children randomly assigned to 8 weeks of treatment with methyl B12 at 75 ug/kg given SubQ every 3 days
- Primary outcome measure CGI-I and the mean at 8 weeks was significantly better (lower) in the methyl B12 group (2.4) compared to the placebo group (3.1) (95% CI 1.2 to 0.2, *P* = .005
- Clinical improvement in CGI-I was significantly correlated with methionine (*P* = .05), decreases in SAH (*P* = .007), and improvements in SAM/SAH (*P* = .007)

Hendren RL, et al. Journal of Child and Adolescent Psychopharmacology 2017 . ClinicalTrials.gov Identifier: NCT01039792.

NAC in Children with Autism

- NAC is an glutamatergic modulator and an antioxidant
- 12-week, double-blind, randomized, placebo-controlled study of NAC in children with autistic disorder
- NAC was initiated at 900 mg daily for 4 weeks, then 900 mg twice daily for 4 weeks, and 900 mg 3 times daily for 4 weeks
- 33 patients (31 male, 2 female; aged 3.2 to 10.7 years) were randomized
- Oral NAC was well tolerated with limited adverse effects
- Compared with placebo, NAC resulted in significant improvements on ABC-I ($F = 6.80$; $P < .001$; $d = .96$)

Hardan AY, et al. *Biol Psychiatry*. 2012;71(11):956-961.

UCSF-IAN Omega-3 Results

- 863 e-mail invitations
- 118 responded
- 57 met eligibility criteria from 28 states
- Recruitment completed in 6 weeks
- 57 teachers contacted and agreed to participate
- 100% completion rate, study finished in 12 weeks
- Results
  - Omega-3: ABC-H: -5.3 points
  - Placebo: ABC-H: -3.4 points *P* = .38, ES = .26
- Implications
  - Internet is a powerful tool for clinical trials
  - Sample size insufficient to judge efficacy of omega-3

IAN = Interactive Autism Network.
Bent S, et al. *J Am Acad Child Adolesc Psychiatry*. 2014;53(6):658-666.

Vitamin/Mineral Supplement and ASD

- RCT of oral vitamin/mineral supplement for 3 months with 141 children and adults with ASD
- Improved the nutritional and metabolic status of children with autism, including improvements in methylation, GSH, oxidative stress, sulfation, ATP, NADH, and NADPH
- The supplement group had significantly greater improvements than did the placebo group on the Parental Global Impression-Revised Average Change (P = .008), Hyperactivity (P = .003), and Tantrumming (P = .009)

ATP = adenosine-5'-triphosphate; NADH = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate.
Adams JB, et al. *BMC Pediatr*. 2011;11:111.

Diet

- Inconsistencies between parent reports and the results of clinical trials for a gluten-free casein-free diet in children with autism with no RCT showing benefit
- Several studies suggest a relationship between non-celiac gluten sensitivity and autism
- Detailed metabolic screening in a Greek cohort of ASD patients revealed biomarkers (urine 3-hydroxyisovaleric acid and serum b-OH-b) in 7% (13/187) of patients for whom biotin supplementation or institution of a ketogenic diet resulted in mild to significant clinical improvement in autistic feature
- Specific carbohydrate diet

Cheng JX, et al. *Adolesc Med State Art Rev*. 2013;24(2):446-464. Catassi C, et al. *Nutrients*. 2013;5(10):3839-3853. Spilioti M, et al. *Front Hum Neurosci*. 2013;7:858. Autism Network for Dietary Intervention. www.autismndi.com/news/advanced-dietary-interventions/the-specific-carbohydrate-diet-scd.html#.U4NJisZ216k. Accessed June 25, 2014.

Microbiota Modulate Behavioral and Physiological Abnormalities Associated With Neurodevelopmental Disorders

(Grade C Mod)

- Demonstrate GI barrier defects and microbiota alterations in the MIA mouse model that is known to display features of ASD
- Oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like, and sensorimotor behaviors
- Maternal high fat diet in mice results in social and synaptic defects corrected by probiotic treatment

MIA = maternal immune activation.

Hsiao EY, et al. *Cell*. 2013;155(7):1451-1463; Buffington SA et al, 2016.

Pancreatic Digestive Enzymes

- Enzyme deficiencies in children with autism result in an inability to digest protein
- The inability to digest protein affects the production of amino acids essential for brain function
- RCT completed but not published
- Biomarker – fecal chymotrypsin

ClinicalTrials.gov Identifier: NCT00881452, NCT00912691.

Balovaptin Autism Tx Study

(Grade I Medium; insuff)

- Works by blocking a brain receptor of the vasopressin receptor that is associated with control of stress, anxiety, affection, and aggression
- 213 high functioning ASD males ages 18 to 45 years. Participants take either 1.5 mg or 4 mg or 10 mg or placebo daily for 12 weeks
- Results are showing improvements on Vineland II composite score, but not on SRS-2 for subjects treated in 4 mg or 10 mg Balovaptan.
- Balovaptan was well tolerated across all doses & no drug-related safety concerns were identified.
- Currently finished Phase II Pediatrics AVIATION study for ages 5-17 for 24 weeks DBPC followed by 52 weeks of open label extension phase.
- Phase III Adult study is also ongoing currently (VIADUCT study)

Bolognani et al., Sci Transl Med, 2019

Other Considerations

- Medical marijuana/THC/CBD and the endocannabinoid systems (Level 4)
- GABA-A (Level 3)
- Vitamins and Mineral Supplements (Level 2)
  - Relatively high doses of Vitamins B1, B2, B3, B5, B6, B12, biotin, folate, C, D, and K
  - Folate instead of folic acid
  - MSM (a good source of sulfate which is low in many ASD)
  - Low-dose lithium (more than 100× below the levels when it is used as a psychiatric medication

THC = tetrahydrocannabinol; CBD = cannabidiol.

Hollander E, et al. *Am J Psychiatry*. 2012;169(3):292-299. Krueger DD, et al. *Neuron*. 2013;78(3):408-410. Han S, et al. *Nature*. 2012;489(7416):385-390. Adams JB. *Vitamins & Minerals*. 2015;4(1). http://autismnrc.org/assets/images/PDF%20Files/vitaminmineral-supplements-for-children-and-adults-with-autism-2376-1318%201000127.pdf. Accessed June 16, 2015.