# Beyond the M-CHAT

## Autism as a Systemic Condition

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# Disclosures/COI

for today's talk...

**Stephen Kahler**

No disclosures or conflicts of interest

**Kristi Wees**

No disclosures or conflicts of interest

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# Today's Talk

## Things to discuss:

**ASD Presentation**

What is Autism, What is MCHAT

The Grandma's Sense

The Tale of Two Children

**Medical Co-Morbidities**

Autism as a Multi-System Condition

Systems Overview

Clinical Findings/Family History

**Specialist Referral and PCP Support**

Who? Genetics Professionals

PKU lessons

When? Red Flags for Referral

How? Ways to help a family Immediately:

TRIAL (Test, Remove Inflamers, Accumulate Data, Listen for Clues )

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# Objectives

## for learning today...

**Objective 1**

Learners will be able to describe medical co-morbidities that can occur with Autism Spectrum Disorder (ASD) and explain the role for the clinical and biochemical geneticist in addressing specific co-morbidities.

**Objective 2**

Learners will be able to:

1) differentiate the presentations of ASD (e.g., gradual awareness, or sudden regression);

2) identify typical and atypical features in the family history and exam;

3) recognize the role of different specialists and lab tests in the evaluation of ASD.

# A is for Autism

How is this condition defined

**DSM - V**

A. Persistent **deficits in social communication and social interaction** across multiple contexts...

B. **Restricted, repetitive patterns of behavior**, interests, or activities...

C. Symptoms must be present **in the early developmental period** (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).

D. Symptoms cause **clinically significant impairment in social, occupational, or other important areas of current functioning**.

E. These disturbances are **not better explained by intellectual disability** (intellectual developmental disorder) **or global developmental delay**. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Source: https://www.autismspeaks.org/autism-diagnosis-criteria-dsm-5

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# A is for Autism

How is this condition defined

DSM - V

Specify if:

- With or without accompanying intellectual impairment
- With or without accompanying language impairment
  - (Coding note: Use additional code to identify the associated medical or genetic condition.)
- Associated with another neurodevelopmental, mental, or behavioral disorder
  - (Coding note: Use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].)
- With catatonia
- **Associated with a known medical or genetic condition or environmental factor**

Source: https://www.autismspeaks.org/autism-diagnosis-criteria-dsm-5

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# Diagnosing Autism

## Cause or Treatment?

There is nothing in the description about causation, untreatability, irreversibility, etc

## How to measure

Various diagnostic criteria—points on a scorecard—reflect attempts to quantify something we don't understand how to measure very well.

## Symptoms and biology

Core Symptoms—communication, social interactions, restricted interests, impaired language and development.

**ONLY biologic criterion is age of onset.**

No mention of diarrhea, seizures, developmental regression or immune dysfunction.

Beyond the MCHAT

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# What is the M-CHAT™

## M-CHAT™

Modified Checklist for Autism in Toddlers

23 Questions

## M-CHAT-R/F™

The Modified Checklist for Autism in Toddlers, Revised, with Follow-Up

20 Questions

A Checklist that is used in pediatric and family medicine exam rooms across the country to screen children for Autism. AAP recommends screening at 18 & 24 month well checks.

Other Autism Screeners:
Ages and Stages Questionnaires SE-2 (ASQ-SE2)
Pervasive Developmental Disorders Screening Test-II (PDDST-II)
Communication and Symbolic Behavior Scales (CSBS)

source: https://mchatscreen.com/
https://www.healthychildren.org/English/health-issues/conditions/Autism/Pages/How-Doctors-Screen-for-Autism.aspx

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# How Autism Presents

## Gradual Awareness

Gradual Awareness

- Chronic
- Slowly emerging
- No Sudden change

## Acute Regression

- Typically in 2nd year
- Antecedents:
  - Feeding difficulties
  - Formula changes
  - Otitis/antibiotic exposure
- Triggers:
  - Infection
  - Fever
  - Inflammation
- Food and Intestinal problems

# Grandma's Sense

**They don't feel right**

Floppy, Stiff, Low Tone, High Tone, Legs pumping, excessive startle

**They are too quiet or cry too much**

High pitched scream or not a peep, Colic, crying multiple hours a day or barely able to rouse to feed?

**They don't respond to my voice like other children**

Are they deaf? Can they hear me? Do they turn toward my voice? Emotional affect in response to voice, micro-twitches in response to speech rhythms.

Why?

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# A Tale of Two Children...

## D-man and Lady-A

Everyone remembers their "starter" patient. The one that makes us pause and question the paradigm of what we have been taught. The one that goes against the textbook definition and charts a path and an encyclopedia of knowledge, all on their own.

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# D–Man

My original patient (from 1992) had significant bowel disease starting in his first year.

After numerous interventions by traditional and non-traditional practitioners he started having semi-normal bowel function at age 8-1/2 years.

He continues on a restricted diet with numerous supplements, but is functioning well, has completed a four-year accounting program at a community college, and is an active consultant to autism programs.

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# LadyA

"Maybe it's autism, we will just need to wait and see if that is what it turns into..."

-Symptoms of "colic" and irritability start at 4-6 weeks of age
-Intermittent Regressor- with environmental triggers, inflammatory events and food exposures
-Diarrhea, Malabsorption, Failure to thrive, Feeding difficulties for first 2-3 years of life.
-Autistic Like Behaviors and self injurious behavior after one year well visit and cessation of breast feeding + introduction of cow's milk
- Clostridia Difficile Toxin A&B positive after year on reflux meds.
-Severe neurological reactions to household chemicals, perfumes and alcohol fumes (hand sanitizer, windex, wet wipes, etc.)
-Elevated Lactate and Pyruvic Acid around 18mo.
-Low Methionine (normal on NBS) and Low total Homocysteine at 18 mo. (normal on NBS)
- WES normal, no VUS's
- Thiamine (B1) responsive
- Today, in junior high, no ASD, straight A's, gifted and talented student, snow skier, ice skater, gymnast, ventriloquist.

# A Clue that led to Genetics...

- **The autism is not classic and/or the diagnosis is not straightforward**
- **Developmental regression**
- **Neurological regression**
- **Seizures**
- **Food intolerances or avoidance**
- **When observed together with one or more other "red flags," lack of learning in autism demands scrutiny**
- **Unusual findings on physical examination including**
- **atypical biochemical finding**

Dr. Marvin Natowicz is a neurogeneticist previously practicing at Mass General Hosp., Boston and the Eunice Kennedy Shriver Center in Waltham, MA where he was the Medical Director of Genetics. He is now a member of the metabolic team at the Cleveland Clinic. Natowicz is specifically interested in metabolic disorders in autism and, in a 1999 Boston based "LADDERS" lecture, enumerated a number of "red flags" which invite investigation into underlying metabolic (including mito) disease in autism:

## Red flags requiring further scrutiny by metabolic clinicians:

1. The autism is not classic and/or the diagnosis is not straightforward when observed by credible specialists. Examples of this are children who may score as autistic or PDD-NOS by DSM-IV criteria because they have language, social and behavioral deficits. However, professionals often say that they have "too much eye contact" or a certain "eye quality" or are "too social" even though their social skills are below expectations for developmental age. Diagnosticians use terms like "atypical autism" or "features of atypical autism," or they may say, it's "not quite autism" but we're not sure what it is either. This is a "squishy" diagnosis.

2. Developmental regression: Because some 25-33% of autism is regressive in the first year of life, some clinicians discard these kids as unworthy of further scrutiny. Loss of previously attained skills is always significant and should be carefully regarded by medical professionals. Video documentation is very helpful.

3. Neurological regression: This might manifest as loss of muscle strength or physical ability, easy fatigue or lethargy. Be on the look out for intermittent loss.

4. Seizures: Some 33% or more of children with autism are expected to show EEG abnormality or seizure activity in their lifetime so many clinicians discard this very important marker for metabolic stress.

5. Food intolerances or avoidance: If foods cause changes in neurological status, this is significant for metabolic disorder. A child who has typical or near typical muscle skills but becomes frankly ataxic upon eating a certain food, may have a "leaky form" or partial defect associated with a given metabolic disorder. For example, children with less advanced maple syrup urine disease (MSUD) can become clumsy after eating foods high in branched chain amino acids (generally proteins). The disorder may be more apparent under circumstances where there is a greater catabolic demand on the body such as during fasting (i.e. overnight) or infection. For this reason, first in the AM urine is often preferred for analysis. This underscores the need to collect urine samples during times of obvious unbalance or muscle loss.

6. Given the proper educational, behavioral and therapeutic supports, children with autism are capable of learning. When children do not learn (or lose cognitive skills), one may first question whether the child is being taught appropriately. If the answer is “yes” or if the educational piece is corrected and the child still does not make progress, metabolic scrutiny is often appropriate. When observed together with one or more other "red flags," lack of learning in autism demands scrutiny.

7. Family history: a second affected sibling cries out for metabolic scrutiny. I would venture to add here that families who have a history of miscarriage along with an affected child, should demand further metabolic work up in their child.

8. Unusual findings on physical examination including:
*growth retardation or excessive growth
*small head circumference esp. if this declines over time relative to over-all-size
*significant motor dysfunction
*atypical biochemical findings [examples include but not limited to low blood $CO_2$, high blood ammonia, liver function abnormalities, creatine phosphokinase (CPK) abnormalities indicative of muscle injury, etc.. Some clinicians feel that values must be at least 2 standard deviations from the mean in order to be significant. Most agree that flagged values (i.e. any value outside the normal reference range) warrent a repeat blood draw for validation.]

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Dr. Marvin Natowicz

# Systems Overview

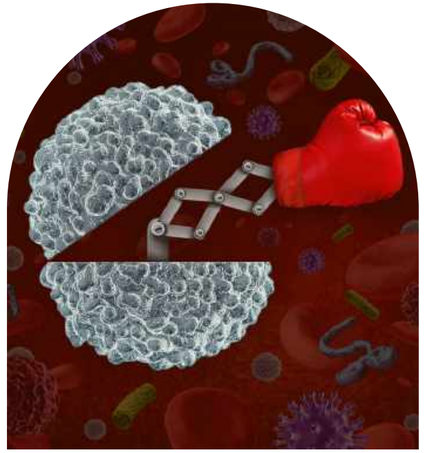
## Multi-System Impact

### Gastrointestinal

Belly Troubles?
Reflux, Constipation,
Diarrhea

### Neurological

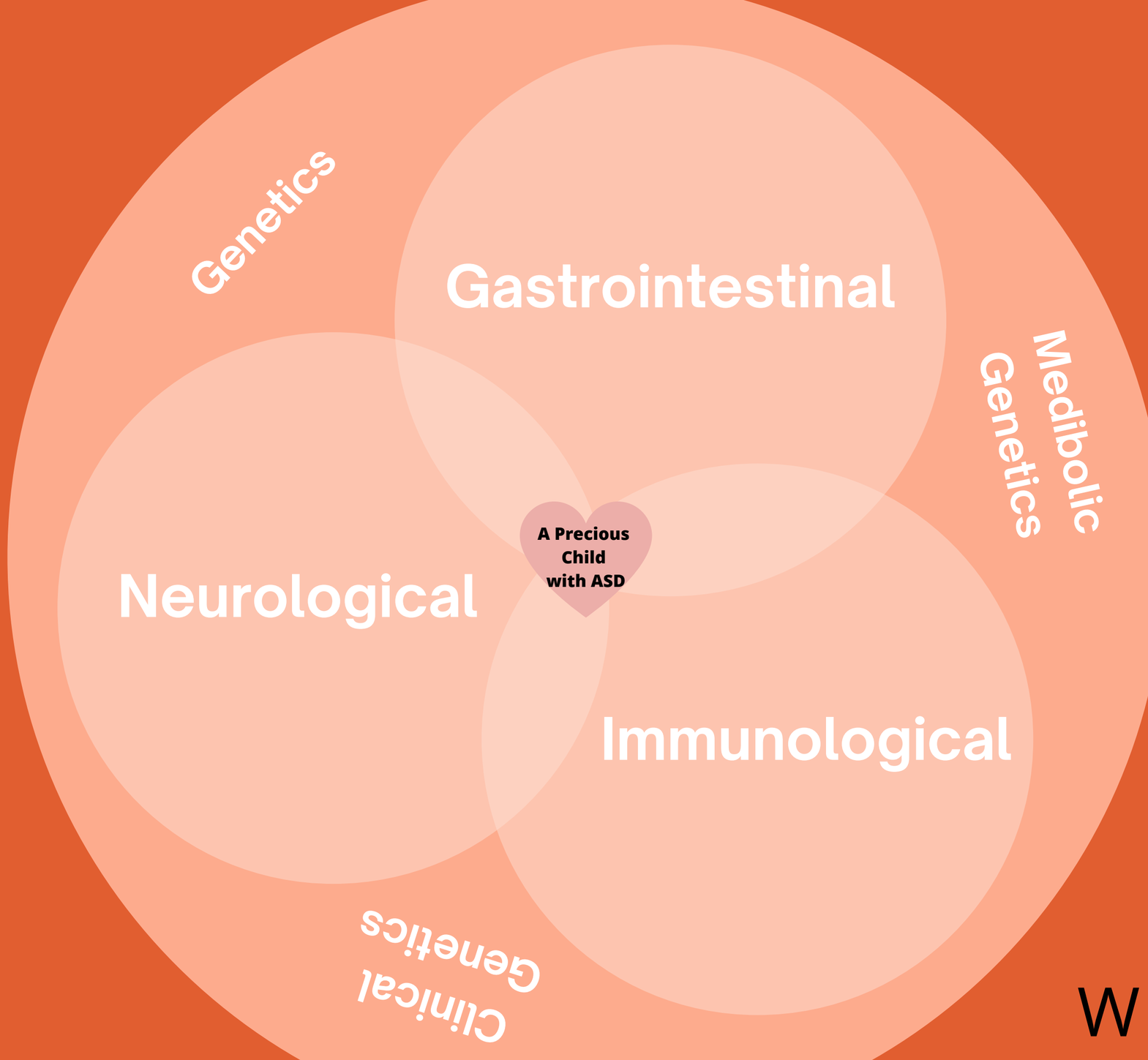
Brain Dysfunction,
Seizures,
developmental &
neurological regression



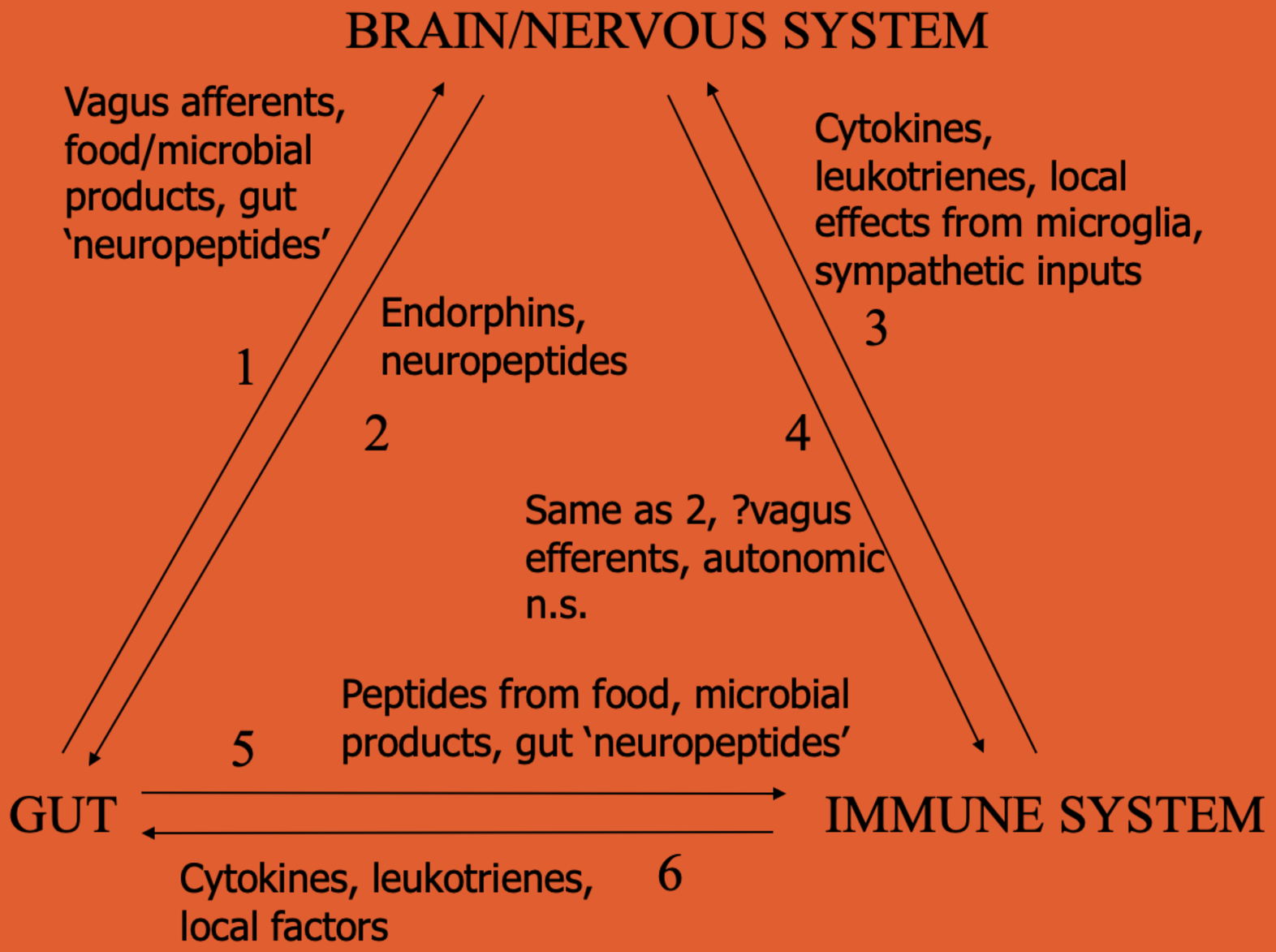
### Immunological

More than just a runny
nose or ear infection

# When 3 or more systems are involved...



# Lines of Communication




**Remember the microbiome**

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# Recurring Themes in the Clinic

- Onset
- Unusual/difficult infancy
- Multiple infections and antibiotics
- Unexplained tachycardia
- Febrile event
- Sudden loss of speech
- Intestinal function, food observations

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# Physical Findings

- Growth generally normal
- Head circumference/brain size often large (2nd 6 months)

# Neuro Findings

- Altered/different ways of perceiving
  - Noises are loud/very acute hearing
  - Smells are interesting/overwhelming
  - Touch is not noticed/painful
  - Vision – too much information?
- Autonomic dysfunction—
  - DILATED PUPILS!
  - Tachycardia
  - Flushing/Red Cheeks/Ears
- CAN DIET CAUSE THESE EFFECTS?
- Disturbed Sleep

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# Gastro Findings

- Feeding problems in infancy
- Abnormal bowel movements--constipation, diarrhea, paradoxical diarrhea
- Food intolerances/allergies
- Restricted diet
- Responses to fasting/bowel rest ± intravenous nutrition
- Pancreas function--response to hormones
- Response to pancreatic enzymes--why?
- Amount/character of digestive juices—stomach acidity, pancreatic secretions

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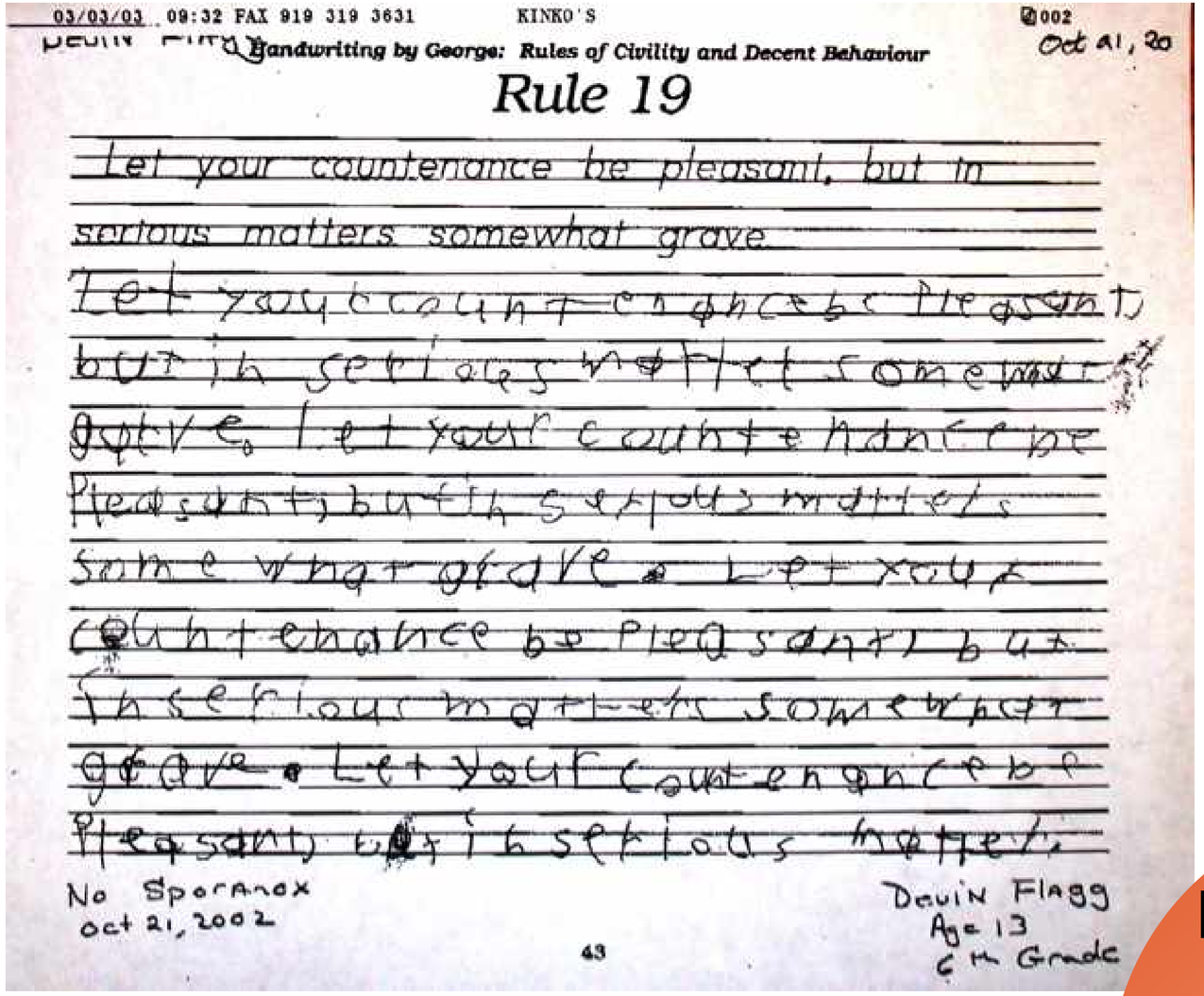
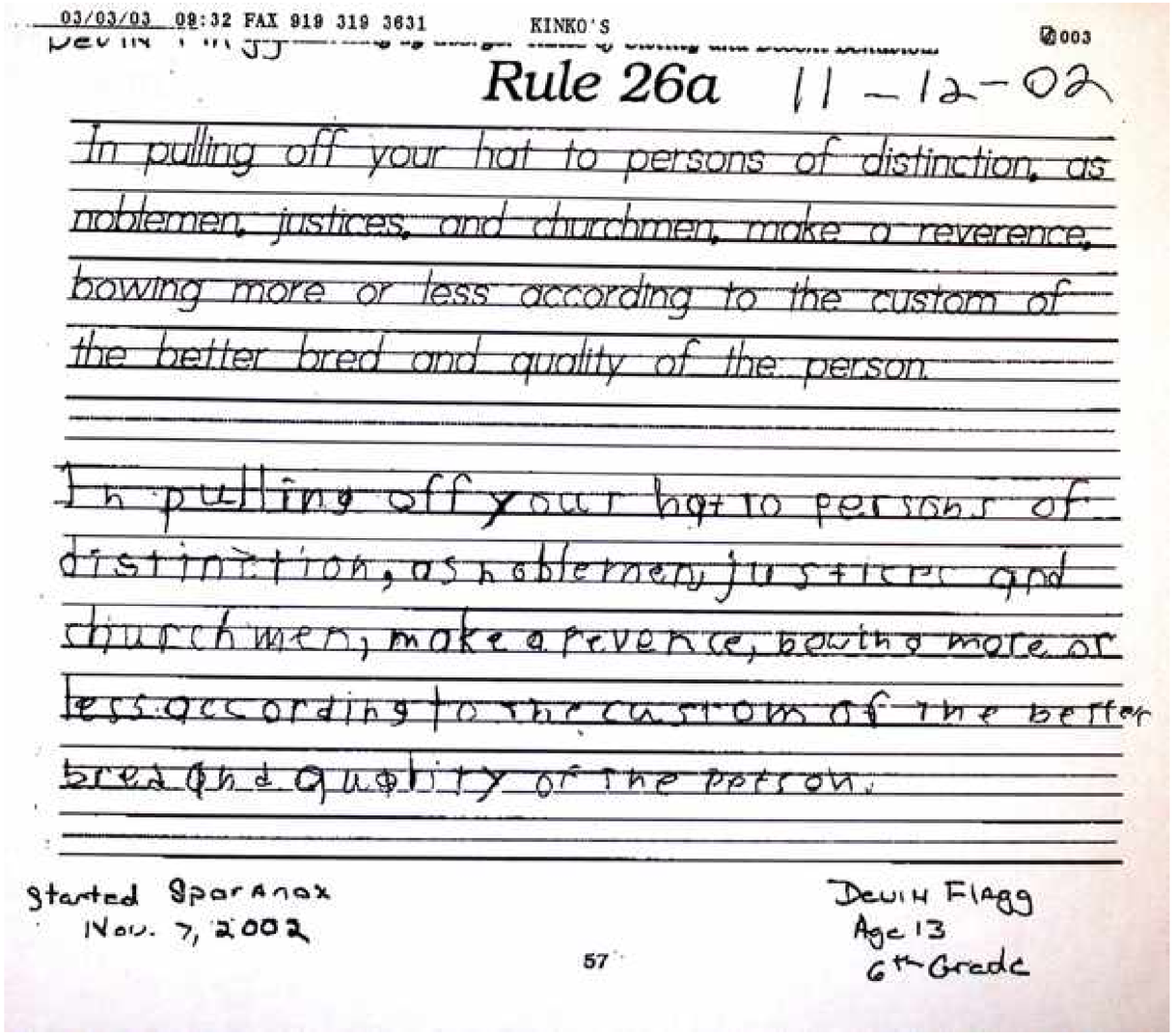
# Handwriting

from D-Man




10/21/02

Itraconazole started 11/7/02




11/12/02

Pizza challenge

# Immuno Findings

- Food Intolerances
- Recurrent Otitis Media
- Persistent Rashes
- Peri-Anal Rashes: Candida
- OR
- Never getting ill
- The "Fever Effect"

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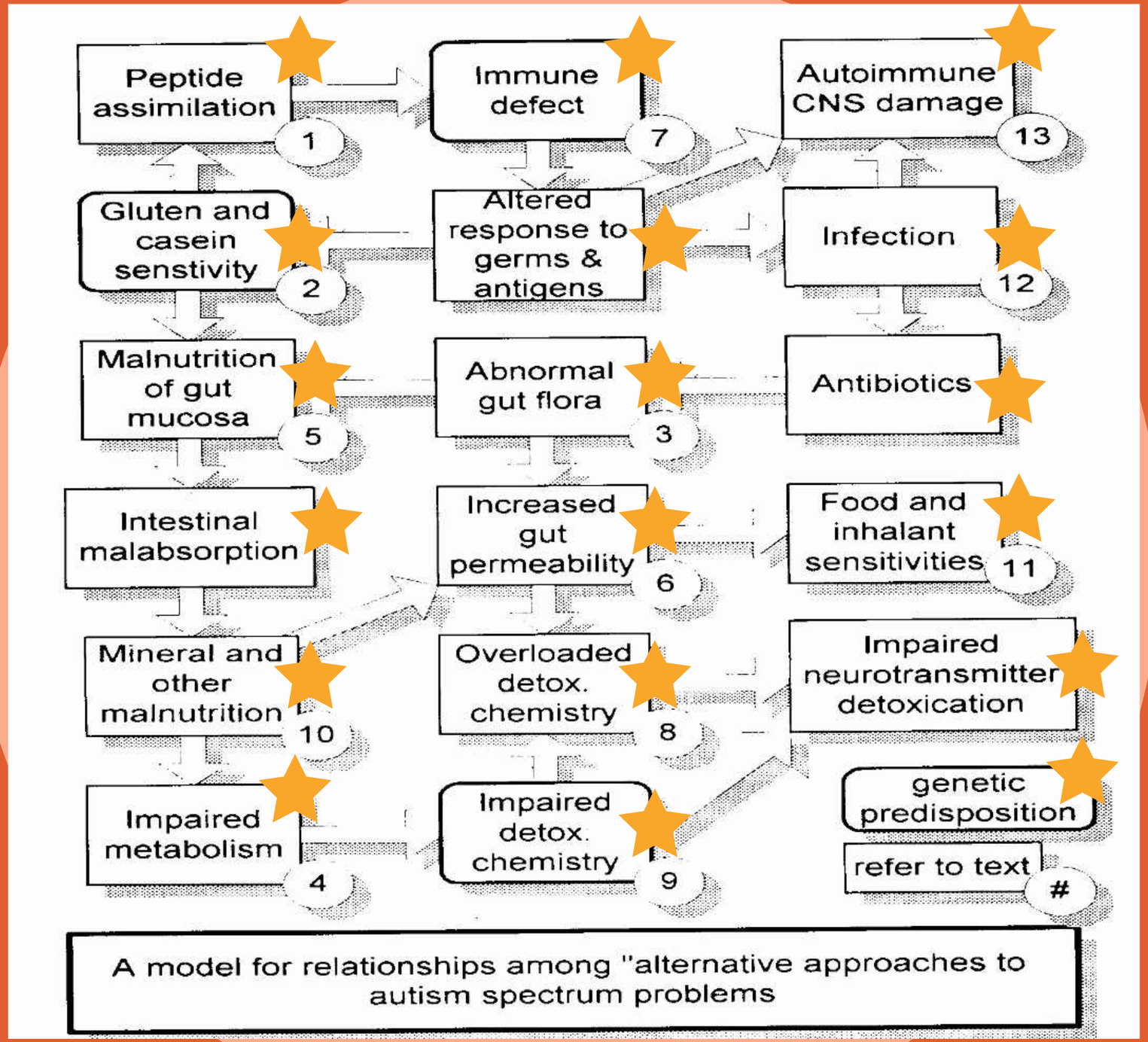
# A model or relationships between the circles

## Baker and Pangborn

First Defeat Autism Now!
(DAN!) Conference, Dallas, 1995.

Stars indicate biological aspects of autism/intestinal disease complex for which there is good evidence.

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# Who?

Who can help? Specialists?

- Geneticist
  - Biochemical Geneticist/Metabolic Geneticist
- Gastroenterologist
- Neurologist
- Immunologist

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# What is Genetic about Autism

- Familial clustering; but recurrence risk not 25% or 50%.
- Male predominance
- Numerous genetic loci--mutations often in genes involved with neuronal proliferation, migration, pruning, synaptic structure; or regulation of gene expression itself.
- No one gene accounts for more than 1% of ASD.
- NO SINGLE MAJOR LOCATION OR MECHANISM.

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# What is Biochemical about Autism

- Simple answer--all behavior and neurological function has a biochemical basis--neural transmission, receptors, responses, memory, etc.
- Persistent theme in autism--Serotonin has something to do with the story
- Platelet serotonin content ( cf. migraine, depression)
- Response to SSRIs (Bob Delong)
- Gut produces 95% of serotonin in body

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# The Lessons of PKU

What lessons can we learn from inborn error of metabolism?

**Genetic**
Completely genetic if you don't know about phenylalanine

**Environment**
Prevention of disease by changing the diet (environment)

**Neurological Harm**
Damage is progressive and irreversible.

**Timing**
Treatment must be started before damage occurs.

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# SPECIALISTS

| Specialist | Possible Problems | Investigations | Possible Findings | Possible Treatments/ Interventions |
|---|---|---|---|---|
| NEUROLOGIST | Disrupted sleep; epilepsy; poor speech; anxiety; impulsive behavior; poor concentration | EEG (preferably overnight); Brain MRI; Lumbar puncture for CSF analysis. | Unstable rhythms; ventriculomegaly; cortical dysplasia; cerebellar atrophy/hypoplasia. | Medications (pharmaceuticals, vitamin co-factors) for seizures, anxiety, aggression, sleep.Propranolol, metatonin, Memenda, omega-3 fatty acids |
| GENETICIST | Significant Family History; Syndromic appearance; | Microarray, Targeted gene analysis, Sequencing Panels, karyotype. | Copy number variants (deletion or duplication); Sequence variation or abnormality; Confirmation of genetic syndrome. | Genetic counseling—interpretation of results. Conveying information regarding recurrence to the parents and other relatives. |
| METABOLIC SPECIALIST (GENETICIST OR NEUROLOGIST0 | Evidence of mitochondrial or other metabolic dysfunction; abnormal brain magnetic resonance spectrometry | Routine biochemical tests; assessment of mitochondrial function, oxidative stress. | Lactic acidosis, increased alanine, increased ammonia (mild); increased glutathione oxidation (GSSG/GSH) ratio. Deficient cofactors (folate, biopterin) or abnormal metabolites in CSF. | Methylcobalamin; carnitine; creatine, and other mitochondrial supplements. Methylfolate or folinic acid supplement. Nacetylcysteine, |
| GASTRO-ENTEROLOGIST | GE Reflux; eosinophilic esophagitis; dysmotility (constipation or diarrhea); Dysbiosis | Endoscopy and biopsies; Stool culture; microbiome assessment | Inflammation, enlargement of lymphoid tissue, ulceration in esophagus, stomach, colon. Crohn's disease, ulcerative colitis, "non-specific" changes (enterocolitis); intestinal dysbiosis. | Anti-inflammatory agents (sulfosalazine, etc). Probiotic supplements, diet changes; |
| NUTRITIONIST | Restricted diet; malnutrition; food intolerances; insistence on specific foods; | Diet and caloric history; assessment for food-derived opioid peptides; | Caloric malnutrition, vitamin D deficiency; peptiduria | Removing offending foods (usually sources of gluten and casein) from diet; avoidance of simple sugars; supplementation of calories, vitamins; |
| IMMUNOLOGIST | Recurrent infections (otitis, enteritis); | Assessment of immunoglobulin levels and cell types (flow cytometry). Cunningham Panel | Deficiency of IgG, IgA, specific T-cell subtypes | Intravenous immunoglobulin supplement (IVIG) |

Kahler

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# When?

When do I refer to a specialist?
When do I refer to genetics?
Should every child with ASD see a specialist?
Does every child with ASD need to see genetics?


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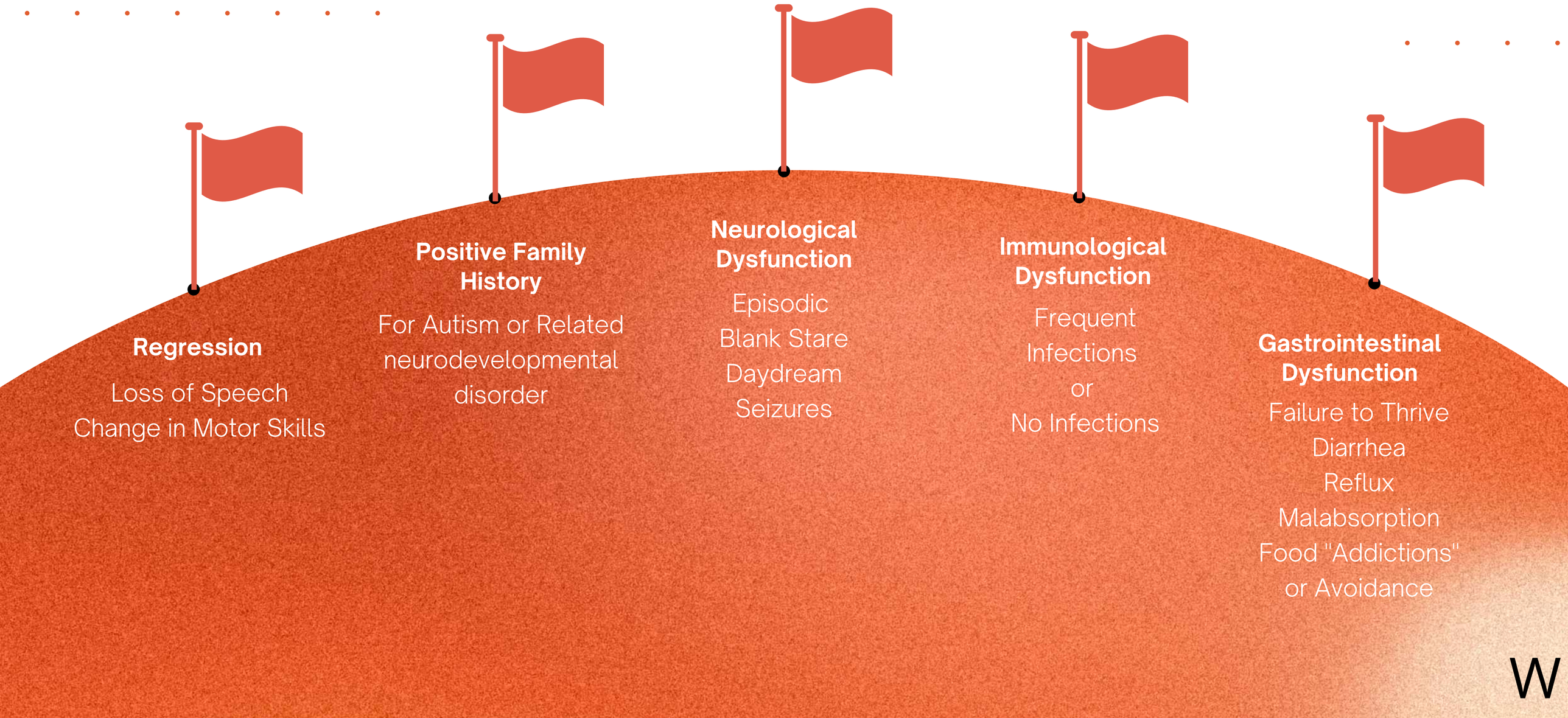
# Red Flags For Referral

## of a child with Autism to Genetics or a Specialist Team



**Regression**

Loss of Speech
Change in Motor Skills

**Positive Family History**

For Autism or Related neurodevelopmental disorder

**Neurological Dysfunction**

Episodic
Blank Stare
Daydream
Seizures

**Immunological Dysfunction**

Frequent Infections
or
No Infections

**Gastrointestinal Dysfunction**

Failure to Thrive
Diarrhea
Reflux
Malabsorption
Food "Addictions" or Avoidance

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# How?

How can I support this family in my office?
What are some things I can do to help this family immediately?
What if the wait is long or the drive is longer to see a specialist?

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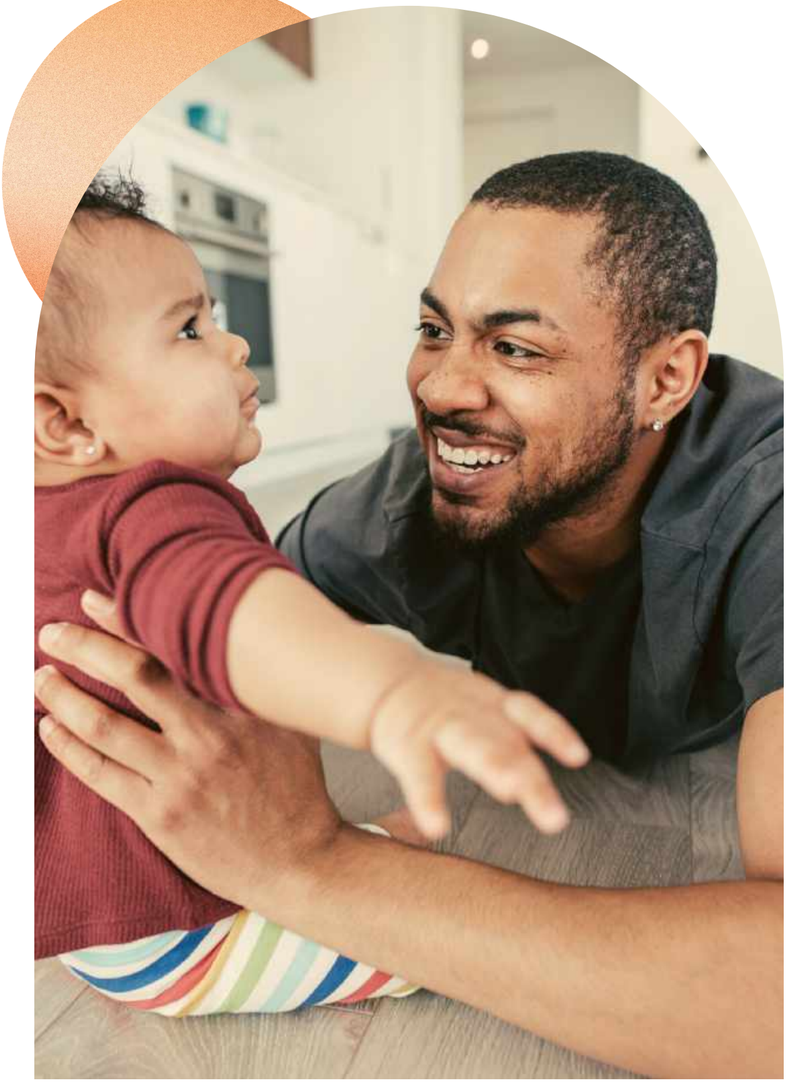
# Good Days and Bad Days?



## TRIAL

: to test the functioning, value, or usefulness of (something)

**TEST**

Measure Biology

**REMOVE INFLAMERS**

Is there a fire that needs put out? Rather take away than add

**ACCUMULATE DATA**

Empower family to gather and share data. ONE CHANGE (variable) AT A TIME

**LOOK & LISTEN FOR CLUES**

What is the next step, the next tweak, the next TRIAL?

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# Some Thoughts to TRIAL: TEST

**Consider preliminary testing…**

**CBC**

**CMP**

**Serum amino acids (just before lunch)**

**Acyl Carnitine Panel**

**Total homocysteine**

Urine creatine metabolites

Urine organic acids

Urine purines and pyrimidines

[Urine oligosaccharides]

[Urine mucopolysaccharides]

# Some Thoughts to TRIAL: Remove Inflamers

- Consider Removing Milk/Dairy and Wheat/Gluten
- Diet changes-- 'Feingold diet' / 'Low Salicylate' / 'Low Oxalate diet'
- Reduce chemical exposure in home environment

- Epsom salt bath ($MgSO_4$)
- Fish oils, other sources of n-3 fatty acids EPA, HEPA
- Oral Thiamine or Thiamine tetrahydrofurfuryl disulfide (TTFD) skin cream
- Probiotics

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# Look and Listen for CLUES

- Limited ability to communicate—leads to misinterpretation of physical symptoms.
- Pounding head, biting self or others—consider headache, abdominal pain, frustration over communication.
- Screaming outbursts—consider reflux, cramps.
- Pounding or clutching abdomen, applying abdominal pressure—consider pain, cramps, etc.
- “Stimming” (self-stimulating behavior)—flapping, humming, ‘vocal tics’—consider this as self-calming behavior.

"Care providers should be aware that problem behavior in patients with ASDs may be the **primary or sole symptom** of the **underlying medical condition**, including some **gastrointestinal disorders**."

Evaluation, Diagnosis, & Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report  Pediatrics 2010 ,v125

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# Thank You


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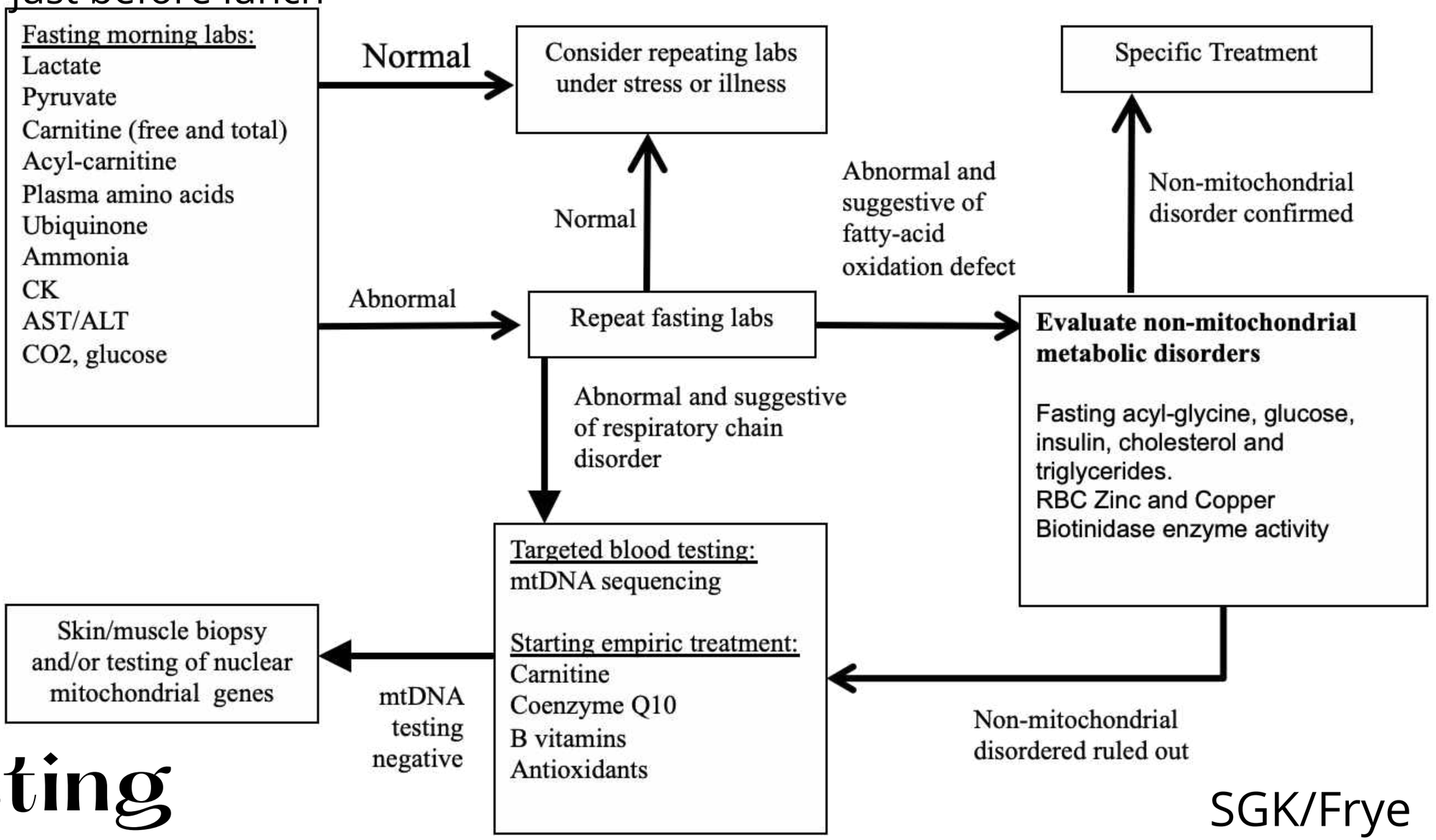
# Mitochondrial Protocol

recommendation:
just before lunch




# Lab Testing

SGK/Frye S

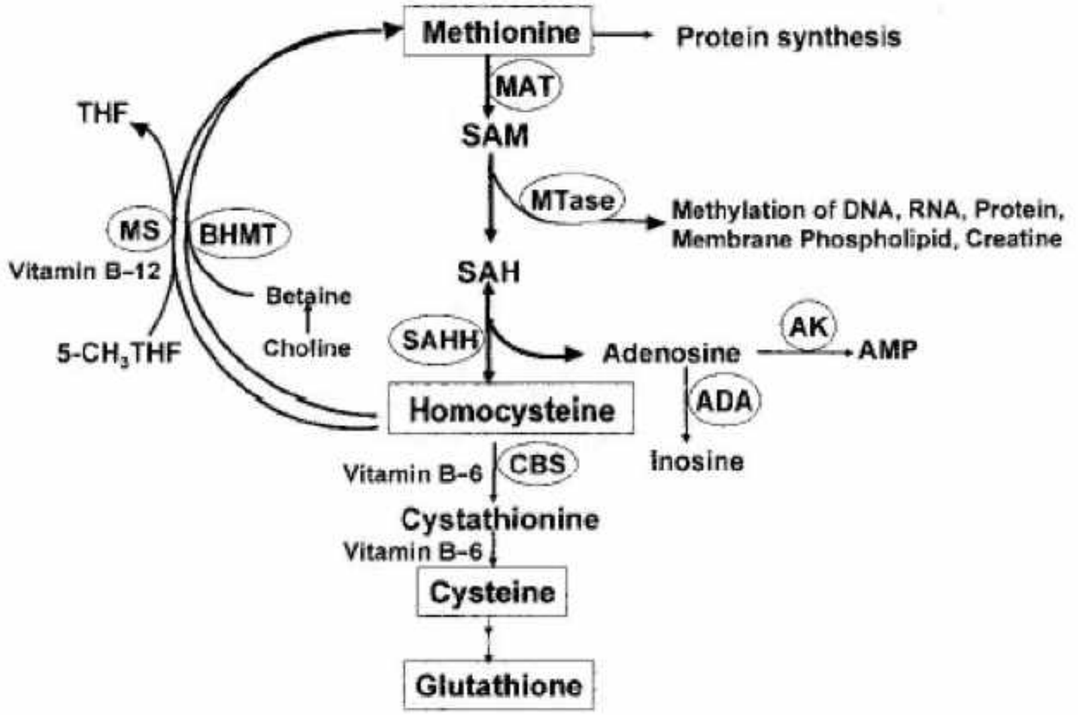



**FIGURE 1.** The methionine cycle involves the remethylation of homocysteine to methionine by either the folate–vitamin B-12–dependent methionine synthase (MS) reaction or the folate–vitamin B-12–independent betaine homocysteine methyltransferase (BHMT) reaction. Methionine is then

Comparison of methionine cycle and transsulfuration metabolites between autistic children and control children[1]

| | Control children ($n$ = 33) | Autistic children ($n$ = 20) |
|---|---|---|
| Methionine (μmol/L) | 31.5 ± 5.7 (23–48) | 19.3 ± 9.7 (15–25)[2] |
| SAM (nmol/L) | 96.9 ± 12 (77–127) | 75.8 ± 16.2 (68–100)[3] |
| SAH (nmol/L) | 19.4 ± 3.4 (16–27) | 28.9 ± 7.2 (14–41)[2] |
| SAM:SAH | 5.2 ± 1.3 (4–8) | 2.9 ± 0.8 (2–4)[2] |
| Adenosine (μmol/L) | 0.27 ± 0.1 (0.1–0.4) | 0.39 ± 0.2 (0.17–0.83)[4] |
| Homocysteine (μmol/L) | 6.4 ± 1.3 (4.3–9.0) | 5.8 ± 1.0 (4.0–5.8)[3] |
| Cystathionine (μmol/L) | 0.17 ± 0.05 (0.1–0.27) | 0.14 ± 0.06 (0.04–0.2)[5] |
| Cysteine (μmol/L) | 202 ± 17 (172–252) | 163 ± 15 (133–189)[2] |
| tGSH (μmol/L) | 7.6 ± 1.4 (3.8–9.2) | 4.1 ± 0.5 (3.3–5.2)[2] |
| Oxidized glutathione (nmol/L) | 0.32 ± 0.1 (0.11–0.43) | 0.55 ± 0.2 (0.29–0.97)[2] |
| tGSH:GSSG | 25.5 ± 8.9 (13–49) | 8.6 ± 3.5 (4–11)[2] |

[1] All values are $\bar{x}$ ± SD; range in parentheses. SAM, *S*-adenosylmethionine; SAH, *S*-adenosylhomocysteine; tGSH, total glutathione; GSSG, oxidized glutathione.

[2–5]Significantly different from control children: [2] $P < 0.001$, [3] $P < 0.01$, [4] $P < 0.05$, [5] $P < 0.002$.

# Methionine Cycle

## Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism[1,2]

*S Jill James, Paul Cutler, Stepan Melnyk, Stefanie Jernigan, Laurette Janak, David W Gaylor, and James A Neubrander*

*Am J Clin Nutr* 2004;80:1611–7.S

# Resources

Autism Research Institute and Cleveland Clinic: CME
https://www.autism.org/cme/