Gender Differences Among Children With Autism Spectrum Disorder: Differential Symptom Patterns

ABSTRACT

The gender ratio among children in the autism spectrum of more than four boys to every girl is widely recognized. The authors present an analysis of gender differences among 79,482 symptoms and strengths in 1495 boys and 336 girls aged 2 to 18 years from parent-identified autistic children reported to a structurally novel anonymous parent-entered online database, Autism360. The data reveal differences that provide previously undetected clues to gender differences in immune and central nervous system and gastrointestinal functional disturbances. Together with published observations of male/female differences in inflammation, oxidative stress, and detoxication, these findings open doors to research focusing on gender physiology as clues to etiological factors in autism. This study exemplifies a research method based on a large, detailed, patient-entered, structured data set in which patterns of individual illness and healing may answer collective questions about prevention and treatment.

INTRODUCTION

In an interview following the 2011 International Meeting for Autism Research (IMFAR), Marisela Huerta, PhD, referred to the gender difference in autism spectrum disorders (ASD) as the elephant in the room. The scientific attention drawn to the preponderance of boys is small when contrasted with the large 4:1 gender ratio generally recognized as exceeding all other common chronic illnesses. This male dominance has been studied from differing vantage points. As in the story of the blind elephant observers, the meaning of ease, is the therapeutic target and that treatment may be guided by questions concerning individual unmet needs for beneficial factors and noxious substances to be avoided or eliminated. The patented information technology supporting this study captures 15 or more specific items (eg, symptoms, signs, life events, quirks, family history, laboratory data, and other elements of a medical narrative) and at least one description of a strength or special skill. The record is patient- or par-

Key Words

Autism spectrum disorders, gender, information technology

Disclosures

The authors completed the ICMJE Form for Disclosures of Potential Conflicts of Interest, and Dr Baker disclosed that he is a cofounder of Autism360.org and receives a stipend for work on the organization’s website. Mr Milivojevich had no conflicts of interest to disclose.
ent-entered, password protected, and anonymous. It is intended to create a portrait of the person’s individuality. The process is open-ended and free of charge; the online user at the interface (Autism360.org) is the immediate beneficiary of an organized medical database. Autism360 also presents treatment options based on the experience of cluster-mates based on proximity analysis. The semantics underlying the database flow from the general acceptance of “spectrum” to refer to autism over the past decade at the same time as contrary efforts to make autism’s definition precise. The dimensionality of “spectrum” is enlarged along two or more axes into which the granular data of Autism360’s members are encoded. A three-dimensional portrait of all the data underlying this report is pictured in reference 7—showing 79,482 symptoms of 1831 parent-identified autistic children aged 2 to 18 years.

METHODS

Autism360.org was established to serve individuals with ASD and their caregivers. The profile items of each individual are represented as intersections in space. The three dimensions of our everyday experience allow us to visualize three attributes (system [S], function [F], and location [W, for “where”) that carry the literal meanings of the patients’ medical narratives. The website interface allows users to drill down to select any profile items they regard as serious, mysterious, vexing, or otherwise helpful to describe their individuality. If, for example, they select constipation, that selection is registered at the intersection between digestive (system-[S]), decrease (function-F), and bowel (location-W) and occupies a point in a conceptual space in which X, Y, and Z axes are S, F, and W. Severity, time descriptors, and other modifiers are encoded as intersections along 21 other dimensions of the system’s hyperspace. The encoding is unseen by the user. The lexicon from which the user chooses narrative details was built over 2 decades in a single general medical practice in which SFW codes were recorded for every word of every patient. The intent of the encoding process was to capture the literal meaning of the words as freely as possible from implications. The aim was to follow the traditional medical imperative of listening to and recording the patient’s own words and withholding judgment until the flow of information is complete. Judgment in this context refers to the diagnostic purpose of a conventional medical interview. Autism360’s intent is to capture as complete a set of characteristics as patients choose to describe the ways they may differ from others—as contrasted with the usual diagnostic intent to categorize a patient based on standard medical diagnostic groupings. Details sufficient to satisfy diagnostic criteria within a larger data set are accessible but not the primary point of Autism360. This technology achieves an interchange among individual and collective data that lets users locate their place in a multidimensional spectrum.

Our hope is to form a system in which the patient’s interest in an accurate, detailed portrait is joined to the collective interest in creating a data structure that reveals patterns. One pattern is based on the proximity of individual data determined by cluster analysis. Clusters permit users to find “others like me” and discover treatment options based on their collective experience. Other patterns are formed by the collective data viewed from various perspectives such as gender. Another kind of pattern may be revealed by associations of data elements in statistical analysis or queries that deliver the collective patterns, for example, of children with or without constipation.

The possibility of forming patterns allows the individual motive to provide good information that serves patient care to further benefit the collective interest in research. Our overriding interest in protecting the confidentiality of the data is preserved by ensuring that the data is anonymous from the start. Only birth year and month are collected, and an alias is substituted for name, freeing the patient (and the system) from any threat to confidentiality.

The current analysis of individual symptom patterns was undertaken based on a previously published analysis of system-function patterns visualized within a selection of eight systems and six functions. The selection was based on three criteria: high data density among the 39 x 42 system-function intersections (Figure 1) and the inclusion of interesting and novel profile items. Abnormal odors exemplifies an interesting category, and strengths (mentioned in psychologists’ reports) are novel in medical records and studies of disease. The 8 x 6 subset (Figure 2) of the more sparse 39 x 42 grid’s totality reduced the total number of sampled profile items from 79,482 to 52,725. The previously published graphical data revealed eye-catching differences within an overall appearance of similarity between boys and girls. To test the reliability of visual presentation and to be more precise about gender differences, we arranged the data in a table in which each row represents one of 713 profile items. A pair of columns itemize the count of each profile item for boys and girls (totals in the database were 1,495 and 3,36, respectively). Thus, the table counts subjects who reported a particular profile item based on gender. As such, the count data lends itself to proportion analysis. A two-sample proportion test (Figure 3) was employed to determine whether or not a statistical difference existed in the proportion based on gender. A normal approximation was used to compute a z score (Figure 4) and a level of statistical significance. When the level of significance was equal or less than a P value of .05, it suggested that the difference between genders for a particular profile item was beyond random chance. In those cases where we suspected a violation in the use of a normal approximation based on a low n, a Fisher’s exact test was employed to compute an exact P value.

We used statistical metrics as a means for sorting Profile Items by z value to rank prevalence of 693 Profile Items with valid P values at the extremes of their distribution (invalid items had no boys, and only one or two girls). In the previous report based on the same data research methodology, we sought eye-catching gender
differences without statistical measures. This approach embodied the data-intensive science dubbed *Fourth Paradigm* by Jim Gray and provided patterns observed from “high altitude” but which may lack the precision required for practical assessments of the differences we seek to detect. Our calculation and reporting of *P* values in this article may err in the opposite direction. The very appearance of *P* values in a scientific publication gives the impression that something is being proved. The use of probability statistics to describe gender differences in this article, however, gives the reader a spectrum of male-to-female prevalence of profile items at the extremes of the distribution of their *z* values (Figure 5). Fisher’s exact test is particularly helpful in many profile items with low prevalence where “eye-catching” differences are difficult to assess in data with asymmetrical numbers of subjects compared.

**RESULTS**

Table 1 presents strengths first and in detail because this is the first report in the medical literature to emphasize such attributes of individuality.

Table 2 displays profile items (PIs) with a higher than expected boy:girl (B:G) ratio among 1495 boys and 336 girls. The names of PIs are terms of self (or child) description used by patients over the years of the coding system. Their path to the current dataset consists of choice of text as shown from drop-down menus presented from Autism360’s lexicon acquired from face-to-face narratives in a medical office setting over many years. The B:G ratio is given as a point of reference against 4.5:1 in the whole dataset. The *P* values are shown to indicate relative rank in the data and as a way to provide a sense of the significance—in the vernacular as well as statistical meaning—of B:G proportions.

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**Figure 1** The 79,482 profile items encoded as intersections among 39 systems and 42 functions from 1831 individuals aged 2 to 18 years from Autism360.

Abbreviation: CNS, central nervous system.
for items with low counts. In this table, “constipation” is the item in the data worth the harvest. A room full of clinicians and researchers experienced in the field of autism were asked, “Who among you believe that autistic boys and girls are very different?” All hands went up. Asked for specifics, “harder” and “weird” came up, but silence otherwise filled the air. Nor was the author (SMB) able to predict that “constipation”—so common in autistic children—should dominate the girls’ data with such a high statistical probability. It matches a theoretical model based on the work of Derrick MacFabe, MD, and the synthesis by McGinnis cited previously, to wit: autonomic regulatory problems deriving from injury to midbrain structures by damage to centers that lie outside the blood brain barrier. The damage may lie in the realm of autoimmune inflammation; this speculation is reinforced by the remarkable pink dominance in symptoms suggesting loss of immune tolerance shown in Table 2. Blue zone data are more consistent with features found in Eliot’s review9 having to do with activity and restlessness. Rectal digging is one of the most troubling symptoms found in autistic children. It has the highest boy:girl ratio of all in the Autism360 data and begs for a theory of causation.

Table 3 lists PIs (other than strength) unique to the pink and blue zones sorted by system. The PI count is the total of unique system-function designations in each system category for the Girls’ and Boys’ data. The P values for each data item fall in a range from .05 to .63 and .052 to .71, respectively. The B:G ratios for each system category bear out the value of including data that are far from statistical significance to provide an overview of B:G differences.

Figure 6 shows all PIs in a comparison of the PI count data in Table 2 with strengths set aside. The graph summarizes findings that point to more central nervous system (CNS) and immune system problems among autistic girls and more behavioral abnormalities among autistic boys.

DISCUSSION

Cognitive difficulties and deficits, loss of immune tolerance, and gastrointestinal troubles are more preva-
lent among autistic girls. Autistic boys show more behavioral abnormalities and increased activity. Words used in years of conversations with parents about their autistic children provide a way to begin to think about these findings. “Drunk” is a word that most often triggers a spark of recognition in parents grasping for a term to express how a once-bright child disappeared into a chaos of dysregulation, silly laughter, and erratic behavior. “Regulatory” helps us identify a theme that runs the entire lexicon of descriptions of autistic attributes. “Drunk” reflects a toxic state. “Regulatory” evokes a brainstem locale that McGinnis indicated was a principle target of toxicity in autism.

The principle etiologic factors of autism are now generally acknowledged to be environmental toxins. Dr MacFabe in his 2012 Nobel Lecture argued persuasively that toxins from gut microbial sources that provoke autistic behaviors in experimental animals injure fundamental biochemical and membrane functions that are gender dependent. Words describing the symptoms of autistic individuals can be combined with those from published literature. The latter offers additional clues to the question how gender differences may arise from exposing cells outside the blood-brain barrier in the brainstem to environmental and gut-derived toxins. Links are offered by the words proclivity, unmasking, and starving that appear in the titles of research findings by a team led by Robert S.B. Clark, MD, and the Safar Center for Resuscitation Research at the University of Pittsburgh, Pennsylvania. Their studies submitted cultured male and female neuronal and lymphoid cells to various stressors, which unmasked different proclivities in cell death (apoptosis) mechanisms. Simply put, male cells underwent injury and rescue in domains of sulfation, glutathione, and oxidative stress featured in the research of Jill James, PhD, and Richard Deth, PhD. In that domain, a vicious cycle of oxidation of methylcobalamin engendered by heavy metals and other toxins cascades to impair N-acetylcysteine–dependent synthesis of glutathione, thus failure of glutathione’s protection against oxidative stress. Male neurons studied by Clark’s team underwent apoptosis via oxidative, nitrositive, and excitotoxic stress with rescue by N-acetylcysteine. The proclivity of female cells was toward protection from such stresses and apoptosis by an entirely different cytochrome c–dependent pathway. The key difference between male and female neuronal and lymphoid cells was the relative incapacity of male cells to maintain intracellular levels of reduced glutathione. The following review of gender differences reveals no comparable findings that implicate fundamental mechanisms. Girls with ASD may be more severely affected because of an increase in CNS apoptosis compared to neurotypical girls, and neurotypical girls may be protected from developing autism because of greater GSH reserve and decreased vulnerability to neuronal apoptosis.

Elise Eliot’s scholarly and engaging book Pink Brain, Blue Brain invites the reader to understand that sex differences in cognition, emotions, and interpersonal behavior are quantitatively small. Her thorough review of the literature documents that boys have higher math scores, spatial ability, and aptitude with maps. Girls have better social, verbal, and reading skills; penmanship; inhibitory control; and planning and organizational abilities. On the other side of the ledger, boys have more difficulty in school (especially in early years), irritability, sleep prob-

Figure 4 Profile items were sorted by z value to produce a table showing the extremes of P values among females (pink) and males (blue).
GENDER DIFFERENCES AMONG CHILDREN WITH AUTISM SPECTRUM DISORDER

problems as newborns, stuttering and other speech impediments, attention problems and hyperactivity, aggression, and risk-taking, while girls have more depression and anxiety. Boys also have significantly higher infant mortality and morbidity:

Boys between two and five years old overwhelmingly select a toy truck, Hot Wheels car, ball, or other suitably male toy when given a choice between one of those and a doll. Three-year-old girls opt strongly for the baby doll, toy kitchen utensils, or toy beauty set (especially if any of the toys is pink).9(p105)

Overall, however, Dr Eliot as a neurobiologist stresses caution in attributing gender differences to “genetics, hard wiring, and constitution” over environmental influences.9 She points keenly to flaws in research that have given testosterone prominence as a major feature in gender differences and mechanisms in autism having to do with too much maleness. This is not to say that testosterone does not play the role implied in the studies reviewed below. Add a recent report that daughters of mothers affected by hyperandrogenic polycystic ovarian syndrome seem to have a higher risk for pervasive developmental disorders, probably due to unbalanced prenatal exposure to high levels of testosterone.19

Let’s shift the literature review of gender differences to focus on biochemical and autism-related factors with a broad environmental view. The number of males born per 100 females (secondary sex ratio) is not stable over time. An increasing trend in Northern European populations in the 18th and early 20th centuries shifted to a markedly decreasing trend from the latter half of the 20th century until the present.20,21 Sudden downward shifts seen in small populations associated with environmental and occupational chemical exposures are consistent with a male disadvantage in responding to toxic burdens.22 A study of adults with Asperger’s syndrome found 24 biomarkers distinguishing affected males from controls and 17 different analytes distinguishing females from controls. Neither gender-specific set of analytes provided separation in the opposite gender. The authors conclude that stratification by gender is essential to studies of autism spectrum conditions.23 A novel autism candidate gene—retinoic acid-related (RAR) orphan receptor-alpha (RORA)—is associated with protecting neurons against oxidative stress, suppression of inflammation, and behaviors similar to those of ASD. One of RORA’s transcriptional targets, CYP19A1 (aromatase), is responsible for converting testosterone to estrogen. The authors propose that in ASD, downregulation of RORA is involved in a self-reinforcing feedback cycle in which testosterone may suppress RORA expression.24 Mitochondria from human females exhibit higher antioxidant gene expression and lower oxidative damage than mitochondria from males; human preterm infants exhibit similar male disadvantage in GSH-dependent response to oxidative stress.26 Human lymphocytes show similar gender-dependent levels of glutathione and glutathione S-transferases.27 During moderate-intensity long-duration exercise, females demonstrate greater lipid utilization and less carbohydrate and protein metabolism than equally trained and nourished males,28 and during strenuous exercise men

The distribution of profile items with low numbers revealed no overrepresentation planned within female- and male-dominant selections.
increase their need for amino acids, whereas women increase mobilization of fat to supplement increases in carbohydrate metabolism.\textsuperscript{29}

Treatment with L-carnitine increased cellular respiration and improved survival in neurons from males, pointing to a reduced capacity or proclivity to utilize free fatty acid in males—demonstrated by reduction in the number of lipid droplets and concentration of triglycerides in the work of Du et al, who concluded, “Specifically, neurons from male mice and rats had an increased autophagic response to starvation associated with increased cell death, rather than increased mobilization and/or utilization of fat associated with increased cell survival as seen in females.”\textsuperscript{24} Cell survival is an attribute appropriate to long-lived neuronal and lymphoid cells that are agents of perception and guardians of memory in an organism. The molecular basis for perception—taking in stimuli from both internal and external environments—differs in those charged with conscious (CNS) vs unconscious (immune) recognition. The gist—decrease in perception and memory required for recognition—is the same. The female disadvantage in the pattern of PIs in this report indicates principal deficits in CNS and immune functions: cognition and immune tolerance, respectively. As such, they offer room for speculating that autistic girls may lack their gender’s protection against oxidative stress associated with alternate mechanisms for apoptosis in neuronal and lymphoid development. That speculation is supported by studies showing gender-based differences in glutathione metabolism in humans\textsuperscript{35,37} and the role of that protection in the face of environmental toxins.

Exposure to the insecticide chlorpyrifos had a greater adverse cognitive impact in boys, lowering working memory scores—a key component of IQ—by an average of 3 points more in boys than in girls. Parental nurturing, on the other hand, was associated with better working memory, particularly in boys. Horton, the author of the study, says, “There’s something about boys that makes them a little more susceptible to both bad exposures and good exposures. One possible explanation for the greater sensitivity to chlorpyrifos is that the insecticide acts as an endocrine disruptor to suppress sex-specific hormones.”\textsuperscript{30} Studies of cerebellar structure and function in rats following gestational exposure to polychlorinated biphenyls (PCBs) revealed neurodevelopmental and behavioral changes greater in male than in female neonates.\textsuperscript{31} Although body mass was not affected at birth, it was lower in PCB-exposed pups vs controls between birth and weaning and more so over time in females than males.\textsuperscript{32} The cholinergic system of female mammals appears more responsive to stress than that of male mammals, where it is anatomically larger, higher in cell density, and more stable with age.\textsuperscript{33} Male (but not female) rats respond to stress with decreased dopaminergic activity in the frontal cortex and amygdala. Females (but not males) showed that stress increased levels of 5-hydroxytryptamine and norepinephrine in CA3 of the hippocampus, where males (but not females) showed increased gamma-aminobutyric acid.\textsuperscript{34} The maturity of newborn girls positively influences their cysteine uptake, which is responsible for 78\% of the variation in their glutathione content. In newborn boys, however, gestational and postnatal ages did not influence cysteine uptake.\textsuperscript{35} In vivo, intracellular total glutathione was higher in female-derived cells and in cells from more mature babies; postnatal age and gestational age had a positive effect on activity of glutathione reductase (GSSG-R). Oxygen (Fio2 \textsuperscript{1} 0.3) was associated with a lower activity of GSSG-R in boys early in life. In human newborn tissue (umbilical cord) subjected to
Table 1 Strengths

| System           | P ≤ 0.05 Pink Strengths | n Boys | n Girls | B:G | P value |
|------------------|-------------------------|-------|--------|-----|---------|
| Behavior         | Ability to infer        | 21    | 11     | 1.91| .01815  |
| Behavior         | Persistent              | 83    | 25     | 3.32| .018    |
| Behavior         | Strong will/desire to do things | 135 | 38     | 3.552632| .012  |
| Behavior         | Good behavior at school | 120  | 34     | 3.529412| .019   |
| Behavior         | Minimal distractibility | 6    | 2      | 3.86  | .018    |
| CNS              | Good awareness          | 38    | 15     | 2.533333| .018   |
| CNS              | Musical                 | 184   | 54     | 3.607407| .018   |
| CNS              | Perfect musical pitch   | 56    | 20     | 2.8   | .018    |
| CNS              | Good comprehension      | 58    | 17     | 3.411765| .018   |
| CNS              | Good communication      | 32    | 10     | 3.2   | .018    |
| CNS              | Good social interaction | 49   | 14     | 3.5   | .018    |
| CNS              | Good visual memory      | 181   | 46     | 3.934783| .018   |
| CNS              | Art—sculpting, modeling | 15   | 5      | 3     | .018    |
| CNS              | Good imitation of gestures | 66   | 18    | 3.666667| .018   |
| CNS              | Reading                 | 133   | 33     | 4.030303| .018   |
| CNS              | Especially bright        | 148   | 36     | 4.111111| .018   |
| CNS              | Notices everything       | 133   | 32     | 4.15625 | .018   |
| CNS              | Singing                 | 151   | 45     | 3.355556| .018   |
| CNS              | Art—drawing             | 120   | 36     | 3.333333| .018   |
| CNS              | Skill: playing/small object | 48   | 16    | 3     | .018    |
| CNS              | Art: painting           | 34    | 11     | 3.090909| .018   |
| CNS              | Good handwriting         | 51    | 15     | 3.4   | .018    |
| CNS              | Skill: doing fine work   | 20    | 6      | 3.333333| .018   |
| Speech           | Good expressive language | 50   | 13     | 3.846154| .018   |

| System           | P ≤ 0.05 Blue Strengths | n Boys | n Girls | B:G | P value |
|------------------|-------------------------|-------|--------|-----|---------|
| Behavior         | Mellow personality      | 117   | 11     | 10.64| .001    |
| Behavior         | Affectionate            | 635   | 104    | 6.11 | .001    |
| CNS              | Mechanical disassembly (taking things apart) | 118 | 16     | 7.38  | .001    |
| CNS              | Mechanical assembly (putting things together) | 124 | 17     | 7.29  | .001    |
| CNS              | Problem-solving skills  | 56    | 5      | 11.20| .001    |
| CNS              | Ability to memorize (photographic memory) | 354 | 61     | 5.80  | .001    |
| CNS              | Good short-term memory  | 61    | 5      | 12.20| .001    |
| CNS              | Knows numbers          | 381   | 65     | 5.86  | .001    |
| CNS              | Memory—numbers         | 113   | 12     | 9.42  | .001    |
| CNS              | Good at math            | 154   | 14     | 10.00| .001    |
| Neuromuscular    | Balance                 | 166   | 25     | 6.64  | .001    |
| Neuromuscular    | Good athlete            | 50    | 4      | 12.50| .001    |
| Neuromuscular    | Physically strong       | 217   | 34     | 6.38  | .001    |
| Neuromuscular    | Physical ability (gross motor) | 173 | 25     | 6.92  | .001    |
| Neuromuscular    | Skill: throwing/catch ball | 109  | 13     | 8.38  | .001    |

Abbreviations: B:G, boy:girl ratio; CNS, central nervous system.
Table 2: Profile Items With a Higher Than Expected Boy:Girl Ratio Among 1495 Boys and 336 Girls

| System | P = < .05 Pink Profile Items | Boys | Girls | B:G | P value |
|--------|-------------------------------|------|-------|-----|---------|
| Behavior | Dependent or clingy (independence problems) | 4 | 7 | 0.57 | 9.9E-05 |
| Behavior | Eats sand | 44 | 20 | 2.20 | .00665 |
| CNS | Attention or focusing problem | 142 | 51 | 2.78 | .00219 |
| CNS | Small head | 2 | 4 | 0.50 | .00219 |
| CNS | Problems with spelling | 43 | 21 | 2.05 | .00235 |
| CNS | Memory lapse | 10 | 8 | 1.25 | .00045 |
| CNS | Developmental delay | 294 | 88 | 3.34 | .00782 |
| CNS | Fainting spell (passed out) | 1 | 2 | 0.50 | .03048 |
| CNS | Family history of ADD or ADHD | 91 | 31 | 2.94 | .03707 |
| CNS | Loss of or poor balance | 5 | 4 | 1.25 | .04263 |
| CNS | Sleepiness (somnolence) | 5 | 4 | 1.25 | .04263 |
| CNS | Poor short-term memory | 54 | 20 | 2.70 | .04902 |
| CNS | Learning disability or problem | 163 | 53 | 3.08 | .01238 |
| CNS | Poor math skills | 4 | 4 | 1.00 | .02047 |
| CNS | Dyslexia | 17 | 9 | 1.89 | .03093 |
| Digestive | Oily bowel movements | 4 | 4 | 1.00 | .02047 |
| Digestive | Constipation | 235 | 74 | 3.18 | .00530 |
| Digestive | Obstipation (intractable constipation) | 1 | 2 | 0.50 | .03048 |
| Digestive | Can't eat chewy food | 3 | 4 | 0.75 | .00789 |
| Digestive | Bloating after eating | 36 | 16 | 2.25 | .01892 |
| Digestive | Allergic stomach | 12 | 11 | 1.09 | .00024 |
| Digestive | Clostridium difficile infection | 5 | 5 | 1.00 | .00952 |
| Digestive | Reflux esophagitis | 2 | 3 | 0.67 | .01598 |
| Digestive | Family history of diverticulitis | 18 | 10 | 1.80 | .01676 |
| Digestive | Family history of gastritis | 9 | 6 | 1.50 | .02962 |
| Eating | Excessive eating of sugar, candy, or sweet food | 39 | 16 | 2.44 | .03667 |
| Eating | Eats lots of vegetables | 26 | 16 | 1.63 | .00982 |
| Emotion | Always frightened or afraid | 1 | 7 | 0.14 | 4.1E-07 |
| Emotion | Hysteria or flipping out | 24 | 12 | 2.00 | .01900 |
| Immune | Allergy, gluten | 118 | 48 | 2.46 | .00023 |
| Immune | Family history of allergies | 116 | 43 | 2.70 | .00304 |
| Immune | Allergy, egg | 100 | 38 | 2.63 | .00374 |
| Immune | Allergy, strawberry | 5 | 5 | 1.00 | .00952 |
| Immune | Sensitivity to bug bites (skin welts) | 30 | 14 | 2.14 | .01949 |
| Immune | Allergy, rice | 9 | 6 | 1.50 | .02962 |
| Immune | Sensitivity to latex | 1 | 2 | 0.50 | .03048 |
| Immune | Allergy, cat | 42 | 17 | 2.47 | .03481 |
| Immune | Allergy, ice cream | 7 | 5 | 1.40 | .03631 |
| Immune | Allergy, infant formula | 7 | 5 | 1.40 | .03631 |
| Immune | Allergy, shrimp | 5 | 4 | 1.25 | .04263 |
| Immune | Cerebral allergies | 3 | 3 | 1.00 | .04885 |
| Immune | Allergy, bug bite | 10 | 6 | 1.67 | .04686 |
| Neuromuscular | Trouble walking | 8 | 12 | 0.67 | 1.3E-06 |

| System | P = < .05 Blue Profile Items | Boys | Girls | B:G | P value |
|--------|-------------------------------|------|-------|-----|---------|
| Behavior | Behavior purposeless | 49 | 3 | 16.33 | .0174 |
| Behavior | Destructive or mean behavior | 86 | 9 | 9.56 | .0217 |
| Behavior | Does not try to communicate with words or gestures | 125 | 12 | 10.42 | .0026 |
| Behavior | Excessively picks nose | 105 | 12 | 8.75 | .0194 |
| Behavior | Inappropriate or repetitive play or behavior | 252 | 42 | 6.00 | .0494 |
| Behavior | Limited interests | 223 | 33 | 6.76 | .0150 |
| Behavior | Like fans or spinning objects | 218 | 27 | 8.07 | .0014 |
| Behavior | Rectal digging | 33 | 1 | 33.00 | .0191 |
| Behavior | Stimming—door closing | 103 | 12 | 8.58 | .0235 |
| Behavior | Stimming—jumping | 138 | 15 | 9.20 | .0043 |
| Behavior | Stimming—running back and forth | 129 | 14 | 9.21 | .0059 |
| Behavior | Takes clothes off inappropriately | 104 | 13 | 8.00 | .0365 |
| Behavior | Unresponsive to school activities | 48 | 3 | 16.00 | .0196 |
| Eating | Picky or poor eater | 233 | 33 | 7.06 | .0067 |
| Neuromuscular | Fidgeting, jumpy, or moving all the time | 197 | 27 | 7.30 | .0094 |
| Speech | Receptive processing problem | 114 | 13 | 8.77 | .0143 |

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; CNS, central nervous system.
oxidative stress (tert-butyl hydroperoxide), only male-derived tissue showed a sustained increase in glutathione. Responses of female-derived tissues were not variable and reversed proportional to the oxidative stress. Considering that glutathione is a central element in the antioxidant defense, these results suggest that specific tissues derived from the baby girl are potentially better protected against an oxidative stress than those derived from the boy.

Words such as drunk and regulatory arise from conversations with parents. “Antioxidant defense” and other references to biochemistry come from literature describing key aspects of gender differences in autism. Together, this vocabulary and perspectives from McGinnis and MacFabe allow us to compare and interpret the differences between boys and girls in the Autism360 data. “Strengths” come first, because clinical assessment benefits from their early mention (if not emphasis), especially in children treated by practitioners focused exclusively on pathology. Especially in nonverbal children (who practitioners may assume do not understand), the erosive repetition of their problems may be repaired by acknowledgement of their strengths. In autistic children, moreover, such talents leverage healing and form the basis for self-confidence and independence—the most valuable treasure that can be given to parents beyond a genetic legacy and life itself. Words spoken directly to a child—even one who shows no indication of attention—are heard and in retrospect may turn out to have mended a fragile spirit. Strengths in both upper and lower sections of Table 1 are elements such as handwriting for girls and math for boys found in neurotypical children. Beyond that, these data are offered to readers as a vocabulary to enrich conversations with parents and children.

**Table 3: Profile Items (Other Than Strength) Unique to the Pink and Blue Zones Sorted by System**

| System   | Pink PI Count | PIs Boys | PIs Girls | B:G   |
|----------|---------------|----------|-----------|-------|
| Behavior | 38            | 3023     | 835       | 3.62036 |
| CNS      | 24            | 1101     | 327       | 3.36697 |
| Digestive| 22            | 419      | 130       | 3.22308 |
| Eating   | 11            | 342      | 105       | 3.25714 |
| Emotion  | 15            | 442      | 140       | 3.15714 |
| Immune   | 44            | 607      | 165       | 3.67879 |
| Neuromuscular | 12  | 772   | 208       | 3.71154 |
| Speech   | 8             | 6706     | 1910      | 3.51099 |

| System   | Blue PI Count | PIs Boys | PIs Girls | B:G   |
|----------|---------------|----------|-----------|-------|
| Behavior | 57            | 7659     | 1373      | 5.5783 |
| CNS      | 12            | 212      | 30        | 7.06667 |
| Digestive| 26            | 631      | 90        | 7.01111 |
| Eating   | 15            | 1016     | 173       | 5.87283 |
| Emotion  | 15            | 835      | 141       | 5.92199 |
| Immune   | 29            | 392      | 49        | 8      |
| Neuromuscular | 3  | 228   | 43        | 5.30233 |
| Speech   | 15            | 1056     | 190       | 5.55789 |

*Abbreviations: B:G: boy:girl ratio; CNS, central nervous system; PI, profile item.*

**CONCLUSION**

Reported here for the first time are detailed data on autistic symptoms gathered via a novel online system that permits patients and parents to benefit from an exchange between individual and collective data. Parents/patients and caregivers collaborate in creating, validating, and maintaining the medical record. The system guarantees ownership and confidentiality to par-
ticipants, who receive a well-organized medical record that includes their strengths with signs, symptoms, life events, and exposures that portray individuality. The invention of a multidimensional coding system for storing all medical data anticipated the use of the word spectrum that directs attention away from “name-it, blame-it, tame-it” medicine toward information and therapies based on special individual needs as contrasted with viewing the disease as the target of treatment. Users’ contributions to a resource of value to others provides added incentive to participate.

Current efforts at computerizing medical records differ little in style from those begun half a century ago. Such past efforts to record, store, report, and analyze personal medical narratives have in the past tended to automate current paper systems rather than envisioning possibilities offered by advances in information technology that permit new ways of capturing, storing, analyzing, and representing personal and collective medical data. Autism360 provides an alternative path that may become necessary as information technology offers increasing access to tools to sort and preserve data. The data presented here reveal hitherto unrecognized clinical aspects of the unbalanced gender ratio in autism. Sorting is the key to finding clinically and scientifically relevant items in a large volume of data. Without a coding structure that permits logical sorting of the words we use to describe our strengths as well as our difficulties, we will not find efficient ways to use our keen human eyes to detect what is most significant. Use of the methods reported here will reveal hitherto unseen gender differences in symptoms that reflect underlying mechanisms in oxidative stress and toxins. The use of z scores to sort symptoms by their relative male vs female provicity gives a novel overview of the texture of clinical expression underlying the 4:5:1 gender ratio in the autism spectrum.

REFERENCES

1. Stone Health News. Autism in girls are the right questions being asked? https://www.stonehearthnewslines.com/autism-in-girls-are-the-right-questions-being-asked/autism/ Accessed September 17, 2013.

2. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009;65(6):591-8.

3. Rivet TT, Matson JL. Review of gender differences in core symptomatology in autism spectrum disorders. Res Autism Spectrum Disorders 2011;5(3):957-76.

4. Baker SM. Autism 360: the development of an online database with patient-entered data. Integ Med Clin J. 2012;10(5):323-32.

5. US Patent Office. US patent 7676384 filed Sept 15, 2000; issued March 9, 2010.

6. Baker SM. Autism spectrum: new metaphor—new paradigm of illness. N A J Med Sci. 2012;5(3):397-9.

7. Hey T, Tansley S, Tolle K. Jim Gray on eScience: a transformed scientific method. Nature 2002;418:632-7.

8. Hey T, Tansley S, Tolle K. Jim Gray on eScience: a transformed scientific method. Nature 2002;418:632-7.

9. Eliot E. Pink brain, blue brain: how small differences grow into troublesome gaps—and what we can do about it. Boston, MA: Mariner Books; 2010.

10. McGinnis WR, Miller, VM, Audhya T, Edelson SM. Neurotoxic brainstem impairment as proposed threshold event in autistic regression. In: Autism: oxidative stress, inflammation, and immune abnormalities, Chabab A, Chabab B, Brown T, editors. Boca Raton, FL: CRC Press; 2013:153-76.

11. Landigren P, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. Environ Health Perspect 2012;120(5):745-58.

12. MacFabe DP. Short chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders Microb Ecol Health Dis. 2012 Aug 24,23: doi:10.3402/mehd.v23i10.25162

13. Du L, Bayir L, Liu Y, et al. Inmate gender-based provicity in response to cytokototency and programmed cell death pathway J Biol Chem. 2004;279(27):28567-70.

14. Du L, Hickey BW, Bayir H, et al. Starving neurons show sex differences in autophagy J Biol Chem. 2009;284(42):28341-42.

15. Manole MD, Tehranian-DePasquale R, Du L, Bayir H, Kochaneck FM, Clark RS. Unmasking sex-based disparity in neuronal metabolism. Curr Pharm Des. 2012;18(35):5946-60.

16. James SJ, Melynky R, Fuchs G. Efficacy of methylcobalamin and folicic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2009;80(3):445-50.

17. James SJ, Rose S, Melynky R, et al. Celluar and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. FASEB J. 2009 Aug;23(8):2374-83.

18. Deth RC. Molecular origins of human attention: dopamine-folate connection. Berlin: Springer; 2003.

19. Palomba S, Mareotta R, EN Cello A, et al. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case-control study. Clin Endocrinol (Oxf). Clin Endocrinol (Oxf). 2012 Dec 27;69(3):285-90.

20. Fellman J, Eriksson AW. Temporal trends in the secondary sex ratio in Nordic countries. Biomedpace Sociobiol. 2011;57(3):243-54.

21. Grech V, Vassallo Agius F, Savona Ventura C. Secular trends in sex ratios at birth in North America and Europe over the second half of the 20th century. J Epidemiol Community Health. 2003;57(1):86-12.

22. Mackenzie CA, Lockridge A, Keith M. Declining sex ratio in a first nation community. Environ Health Perspect. 2002;110(10):1325-8.

23. Schwartz E, Guest PG, Rahimoun H, et al. Sex-specific serum biomarker patterns in adults with Asperger's syndrome. Mol Psychiatry. 2011;16(12):2112-20.

24. Borras C, Naste J, Garcia-Sala D, Lloret A, Failldio PV, Vina J. Mitochondria from females exhibit higher antioxidant gene expression and lower oxidative damage than males. Free Radic Biol Med. 2003;34(6):546-52.

25. Hamon I, Valdes V, Franch P, Buchweiller MC, Fresson J, Hascoet JM. Gender dependent differences in glutathione (GSH) metabolism in very preterm infants. Arch Pediatr. 2012;19(8):247-52. French.

26. van Linsbouw EM, Peters WH. Age and gender dependent levels of glutathione and glutathione S-transferases in human lymphocytes. Carcinogenesis. 1998;19(10):1873-5.

27. Tarnopolsky MJ, MacDougall JD, Akinson SA, Tarnopolsky MA, Sutton JR. Gender differences in substrate for endurance exercise. J Appl Physiol. 1990;68(1):308-12.

28. Lamont LS, McCulahon AJ, Kalhan SC. Gender differences in the regulation of estrogenic activity metabolism. J Appl Physiol. 2003;95(3):1529-65.

29. Hutton MK, Kahn LG, Perera F, Barr DB, Rush V. Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory? Neurotoxicol Teratol. 2012;34(6):534-41.

30. Nguon K, Baxter MG, Sajdel-Sulkowska EM. Perinatal exposure to polychlorinated biphenyls differentially affects cerebellar development and motor functions in male and female rat neonates. Cerebellum. 2005;4(3):271-6.

31. Du L, Hickey RW, Bayir H, et al. Starving neurons show sex differences in autophagy J Biol Chem. 2009;284(42):28341-42.

32. Nguon K, Baxter MG, Sajdel-Sulkowska EM. Perinatal exposure to polychlorinated biphenyls differentially affects cerebellar development and motor functions in male and female rat neonates Cerebellum. 2005;4(3):271-6.

33. Rhodes ME, Rubin RT. Functional sex differences ("sexual dimorphism") of central nervous system cholinergic systems, vasopressin, and hypothalamic-pituitary-adrenal axis activity in mammals: a selective review. Brain Res Brain Res Rev. 2009;59(1):112-22.

34. Luine V. Sex differences in chronic stress effects on memory in rats. Stress. 2002;5(3):205-16.

35. Lavoie JC, Rousseau E, Truttmann AC, Cheses P. Postnatal gender dependent maturation of cellular cytostatic uptake. Free Radiol Res. 2002;36(6):587-7.

36. Lavoie JC, Cheses P. Gender related response to a tert-butyl hydroperoxide-induced oxidation in human neonatal tissue. Free Radiol Biol Med. 1994;18(3):307-15.

37. Lavoie JC, Cheses P. Gender and maturation affect glutathione status in human neonatal tissue. Free Radiol Biol Med. 1997;23(4):348-57.