Abstract – type

(Please see my comments below in bolded parentheses. If your target audience is medical professionals and you hope to get this published by a respected medical journal, then I would suggest adding the specifics I request. If not, feel free to simply ignore my requests for more info; I'm a perfectionist. I do think you can get away with the existing lack of specifics and still have an informative article. Also, I was able to edit out a lot of redundancies, hence the relatively short length of the article now.)

Autism Spectrum Disorders (ASDs) are among a cluster of cerebral diseases involving impairment in communication/social interactive skills, mood, attention, cognitive and adaptive skills and cognitive functions. That is, a set of neurodevelopmental impairments causing the inability to connect on a human level. ASD is characterized by repetitive, cyclic and obstructive behaviors with symptoms stemming from a convoluted geno-/phenoptype relationship whereby pre-existing neurodevelopmental liabilities interact with the child's environment **(Examples? The article you pasted here is a government article without examples aimed at layman.)** In responsive modification, the child typically develops compensatory tactics and defense mechanisms **(Examples, please?)**. Forthcoming studies of children at high genetic ASD risk defined by an older diagnosed sibling are discovering developmental corridors to phenotype manifestation **(Example?)**.

[Developmental pathways to autism: A review of prospective studies of infants at risk]

ASD is severe in terms of incidence, morbidity and societal impact, and while precise organic origins of the brain disorder remain a mystery, principle discoveries suggest that both genes and

environment influence the development of autistic behavior **(Like what? What influences and factors?**). Environmental factors **(Examples, please?)** are thought to interact with the infant's genes **(How so? Please explain?)** and cause anomalous deformities in cerebral and neuronal development and operative connectivity.

[Autistic spectrum disorders: A review of clinical features, theories and diagnosis]

Children who fall on the autism spectrum display concurrent sense-processing complications **(Examples, please?)** clinically pursued by self-modifying mediation **(Examples, please?)**. Contemporary therapy utilizes sensory interventions **(Examples, please?)** utilizing various hypothetical paradigms **(Which?)** that hone in on differing goals by deploying a multiplicity of sensory modalities consisting of remarkably disparate procedures **(Examples, please?)**. Earlier evaluations studied the effects of sensory interventions without recognizing such empirical contradictions.

[A systematic review of sensory processing interventions for children with autism spectrum disorders]

ASD diagnoses are typically delayed **(Why so and at what age is the typical diagnosis?)**, causing unrealized treatment opportunities during the formative period of development. Our investigation extrapolates previous assessments of age-related factors at ASD diagnosis, offering clinical research recommendations, programs, and early detection methods.

[Explaining differences in age at autism spectrum disorder diagnosis: A critical review]

Mutations **(Examples, please? What kind of mutations?)** deform typical neurodevelopment in utero through adolescence via gene composites involved in exuberant synaptogenesis and axon motility. Recent advancements in neuroimaging investigation offer crucial knowledge re pathological brain deformities in ASD in vivo patients. The amygdala is the limbic system's quintessential element involving the affective loop of the cortico-striato-thalamo-cortical circuit in cognition. The nucleus accumbens is the second most important structure related to the social-reward response in ASD **(Related how? Specifics?)**, hence ASD's popularity in neuropathological and neuroimaging studies.

[A Short Review on the Current Understanding of Autism Spectrum Disorders]

A higher rate of ASD diagnoses are consistently found in males over females, in spite of which egregiously little research has sought the causes for an inconsistency whose understanding could prevent or treat ASD in both sexes.

[Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority]

Studies of heredity have unearthed hundreds of gene deviations in autism with radically differing risk effects habitually associated with similar conditions **(Examples of conditions pls?)**. However, numerous variations coalesce on mutual biological pathways **(Which?)**, indicating characteristically-pervasive autism traits including aetiological heterogeneity, variable penetrance and genetic pleiotropy.

[Autism Genetics Opportunities and Challenges for Clinical Translation]

Introduction – type

Researchers believe typical ASD symptoms in children should be considered as ASDs, while adult symptoms should not. Few behavioral indicators are diagnosed in the child's initial year, emerging mostly in the second.

[Developmental pathways to autism: A review of prospective studies of infants at risk]

According to the *DSM-5*, ASD sufferers react inappropriately to conversational cues and engage in abnormal routines and inappropriate obsessions rather than in loving relationships (American Psychiatric Association, 2013). ASD patients present the gamut of cognitive aptitudes, from acute intellectual retardation to remarkable intelligence. The DSM-5 does not, however, include postponement of lingual acquisition as a core ASD symptom as not all ASD sufferers display this trait. Among disorders on the autism spectrum, the eponymous affliction is the most acute, differing from other neurodevelopmental disorders such as Asperger's Syndrome (AS) and Pervasive Developmental Disorder Not Otherwise Specified (PDD–NOS) by said delay in language expansion and the severity of cerebral/behavioral deformities.

About 20 per 10,000 children suffer from ASD. Research utilizing functional magnetic resonance imaging (fMRI) on the brains of ASD sufferers suggest a substantial decrease in long-distance connectivity. Microstructurally, disturbance of brain development is caused by the atypical adaption of cell division, apoptosis and an elevated inflammation of neurons. Recent studies observe both hypo- and hyper- connectivity issues in autistic children's brains depending on age-related factors **(Examples pls?)**, including a child of three mos. at high risk for developing autism

displaying elevated connectivity contrasted with low-risk children, a variant dwindling between ages six and nine months. Findings imply autistic brains suffer from morphological deformities including premature overgrowth of brain organs including the frontal cortex, amygdala and cerebellum, for at six-months the cephalic circumference of ASD infants accrete rapidly when contrasted with typical infants, but decline at adolescence, resulting in typical adult cerebral mass and volume.

Mounting evidence suggests the significance of mirror neurons--brain cells activated when an individual executes and observes a motor action. Mirror neurons affect other individuals' recognition of motor acts and the regulation of social, emotional and cognitive tasks. The mirror neuron system allows individuals to recognize others' motor actions, engendering social cognitive facilities such as empathy, sympathy, compassion and regret while enabling coordination of the motor cortex and higher visual processing brain areas implicated in speech, memory and motion planning.

Evidence of deficiencies in the mirror neuron system in ASD children derive from the gamut of imaging-techniques including fMRI, electroencephalography (EEG) and electromyography (EMG). Studies proved that mirror neuron activity is deformed in ASD children, obstructing their understanding and recognition of others' motor activity.

The genetic design of this neurodevelopmental disorder proves intricate via whole-exome sequencing (WES) and cytogenetics, likewise studies of twins and families suggest ASD's

heritability is more than 80%. Principal ASD-associated syndromes are fragile X syndrome (FXS) and tuberous sclerosis (TS), both with similar pathophysiological processes **(Examples?)** to those of ASD including deviant mRNA translation and an elevated synthesis of protein. FXS is an X-linked genetic disease caused by the inconsistent increase of the FMR1 gene's multiple CGG repeat and by abnormal facial features **(Specifically?)** as well as variously severe **(Specif?)** cognitive deficiencies. TS, however, is an autosomal-dominant disorder caused by mutation in either TSC1 or TSC2 genes presenting as epilepsy, learning challenges and social-interactive issues. More than 40% of patients with TS also suffer from ASD, hence the elevated incidence of epileptic seizures in both ASD and TS sufferers.

Whole-exome sequencing (WES), chromosomal microarray and selective-candidate gene-analysis are the most prevalent methods for identifying ASD-predisposition genes. WES recognizes new or rare genetic flaws in various heterogeneous disorders such as ASD. A recent study of 928 patients showed that ASD is linked to the intensely disruptive de novo mutations in brain-expressed genes.

[Autistic spectrum disorders: A review of clinical features, theories and diagnosis]

A fundamental component of ASD-related behavioral/functional performance is faulty sensory processing. In 1974 Ornitz reasoned that defective sensory modulation derives from the stereo-typic or repetitive activities of ASD children in their attempt to heighten arousal (sensory-seeking) or to self-calm. Clinicians ascribe repetitive behaviors including twirling, rocking and spinning to sensory-processing problems, discovering that children with ASD and other stereotypical

behaviors suffered far greater sensory-processing problems (d = 2.0) than controls. Rigidity, e.g. the refusal to switch to a new activity or behavior with preference for regimen/sameness might also be triggered by hyper/hyporeactivity.

ASD-related sensory-processing issues may also affect children's diurnal functional performance including eating, sleeping and bath-/bedtime behaviors. Selective eating in children is often accompanied by gustatory and/or olfactory over-sensitivities leading to specific food antipathies. Hyperreactivity and taste-aversion often cause anxiety/rigidity re ingestion, evolving into anxious/disruptive eating behaviors. Sensory-processing issues may also upset the patient's sleep cycles as sensory modulation issues in ASD children are linked to unstable sleeping patterns, specifically with entering REM, with 50% to 80% of children with ASD afflicted. Additional studies are required to determine how sensory processing/hypo-hyperreactivity influences self-modulation and stimulation.

[A systematic review of sensory processing interventions for children with autism spectrum disorders]

Autism is distinguished by: (i) a qualitative deficiency in societal communication via non-verbal behaviors including eye-contact, hand-gesturing and physical deportment, leading to the failure to bond and a lack of spontaneity, interest-sharing or social/emotional reciprocity; (ii) qualitative impairments in social communication manifested by retarded lingual development without non-verbal compensation, difficulty initiating and maintaining dialogue, repetitive and stereotypical language and a lack of creative invention, imagination, and imitative play; (iii) a limited interest

repertoire, object or topic obsession, a slavery to dysfunctional ritual/regimen/routine, stereotyped motor mannerisms and a fixation on object parts or aspects rather than gestalt. Common are sensory aberrations including hypo-/hypersensitivity and preoccupation with certain sensations. Lack of imaginative play implies problems with idea-generation essential to human bonding.

Numerous factors cause a decline in the referral-age and diagnosis of autism: (i) heightened detection in healthcare professionals for early autism symptoms, leading to earlier recommendation to pediatric and child-development experts; (ii) increased public and media concern involving publication of memoir and biographical journalism including depiction of pediatric ASD behavior, leading to parental help outreach.

Screening methods **(Specifically, which?)** applied to both referred and general populations (Checklist for Autism in Toddlers (CHAT)) have identified autism as early as 18 months. However, in the sole general-population study to date, while the CHAT screen presented a high positive predictive significance, its sensitivity was insignificant and cannot be recommended for general population screening at one point in time.

The diagnosis of autism at two years human age is less accurate/stable than that of related ASD, yet preliminary response should not be impulsive as working diagnoses are in most cases refined over time in conference with parents. Medical evaluations must identify difficulties in early non-verbal interactions characteristic of children with ASD from two years on. The particular

syndrome presenting in a two-year-old with ASD may vary widely from a more examplar four or five years old. Particularly, explicit repetitive and/or stereotyped behaviors may be the minority, although when concordant with social/interactive deformity strongly indicate ASD.
[Practitioner Review: Diagnosis of autism spectrum disorder in 2- and 3-year-old children]

Re cerebral architecture in ASD patients, both frontal and temporal lobes are notably disrupted, the amygdala particularly influential in cognition as proved by numerous neuropathological and neuroimaging studies **(Cite this?)**. The medial temporal lobe anterior to the hippocampal construction is essential for declarative memory (conscious recollection of facts and events) and determines anti-social/social behavior in ASD patients. The amygdala is the core of the limbic system and affective loop of the cortico-striato-thalamo-cortical circuit, determining eye-contact and facial recognition/motion. Amygdala injury manifests in fear-processing, memory-modulation with emotive content and eye-contact with the human visage. Results in individuals with amygdala lesion mimic ASD phenomena as the amygdala processes somatosensory, visual, auditory, visceral, and synesthesia inputs, channeling efferents through chief conduits the stria terminalis and ventral amygdalofugal pathway. The amygdala comprises 13 nuclei which, histochemically, are divided into three subgroups: the basolateral (BL), centromedial (CM) and superficial groups. The BL group functions as a node-connecting sensory stimuli to upper social cognition, linking the CM and superficial groups with reciprocity to the orbitofrontal cortex, anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC). The BL group is neurologically responsive to other's facial and bodily actions, a sensitivity absent in the remaining two groups of amygdala. The CM group is comprised of the central, medial, cortical nuclei and

periamygdaloid complex, innervating the majority of the brain stem's visceral, autonomic and effector regions while providing a vital output **(output of what?)** to the hypothalamus, thalamus, reticular and ventral tegmental regions. The superficial group includes the nucleus of the lateral olfactory tract **(I could not find a way to change the last sentence. I think this is the only sentence that I couldn't figure out a way to change. I am sorry.)**

Neurochemistrial investigations have revealed in the amygdala both an elevated opiate and benzodiazepine/GABAa-receptor density including cholinergic, dopaminergic, noradrenergic and serotonergic cell bodies and pathways. Because a population of aggressive patients with temporal epilepsy experienced decreased aggression following the bilateral stereotactic ablation of basal and corticomedial amygdaloid nuclei, amygdala function in emotional processing, specifically rage, has been studied with confirmation for amygdala deficit in ASD patients. Post-mortem investigations revealed amygdala disease in ASD patients contrasted with age- and sex-matched controls. Neuronal smallness and heightened cell density in the central, cortical and medial nuclei of the amygdala were found in patients with ASD.
[A Short Review on the Current Understanding of Autism Spectrum Disorders]

The oft cite 4:1 ratio extrapolates an average from international studies, the male predominance non-exclusive to ASD, however, as studies dependably document greater prevalence of attention deficit/hyperactivity and similar developmental disorders in males over females. The ratio's variance is in fact due to variance in identification methods, as the numbers vary radically from 2:1 to 7:1. Interaction with IQ also determines variability with a lower instance of sex-bias in

cohorts with a lower mean IQ than in “high-functioning” partners with a higher IQ, an interaction exacerbated by a lower mean IQ in ASD subjects compared to males, further inflating gender-prejudice .

Lastly, studies tracking the younger siblings of ASD patients suggest investigative prejudice causes an overemphasis on gender-bias, particularly in the high-functioning control. Self-advocates declared timeless and precise diagnoses an “essential need.” Despite diagnostic variance, a gender disparity in ASD predominance remains 2:1–3:1, urging the investigation of sexual dimorphism re the symptomatology of ASD.

The “female protective effect” (FPE) suggests ASD females are at less risk to certain ASD symptoms **(Which symptoms?)** than affected males. FPE has in other disorders such as clubfoot been ascribed to a clear gender-prejudice as genetic research of ASD cohorts have discovered a greater liability of de novo copy number variation (CNV) and de novo loss of function-point aberration in ASD females than in male counterparts. In addition, inherited small CNV are transmitted more often from unafflicted mothers than counterpart fathers.
[Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority]

The clinical benefits of early detection imply the supremacy of parental intervention re autistic children. Heightened parental intervention dates back three decades, encouraging learning in ASD children. Parents trained as “co-therapists” in consistent interventional handling and

modification of child ASD behaviors enhance formative pediatric social interactions including heightened skills (**Examples, please?**) and confidence, in addition to lessening parental/filial stress. Group parental skill coaching has been proven to promote communal support. Metrics of parental intervention in pediatric development must include: pediatric developmental improvement, parental–filial communication, parental understanding, outlook and anxiety, familial cohesion and cost-benefit analysis.

The majority of assessments re timely parental intercession have lacked systems, thus disparaging their scope and validity as they included uncontrolled studies that relied on single-case studies without clinical precision, applicable universality or methodological compliance, often omitting statistics that didn't benefit their prognosis. Smith employed a restrictive foundation of result-contrast by favoring children's cerebral performance while knowing the preponderance of autistic children are mentally retarded.

The New York State Department of Health performed the most responsible clinical study of timely autism intervention allegedly to develop scientific procedural bi-laws, but flagrantly failed to investigate parental intervention. Other self-motivated clinicians made ostensibly methodical studies of randomized controlled trials of parent-arbitered timely intervention by revealing only child-related results, knowing that parental intervention would hurt their medical practice by removing their own importance.

[Parent implemented early intervention for young children with autism spectrum disorder: a systematic review]

In attempt to understand the genetic systems engendering ASD-risk, researchers have studied various inflicted families including those with con-sanguinity, single-(simplex family) and multi-affected family members with ASD, often spanning numerous generations. Employing WES in ASD-affected families, particular abnormalities were discovered in AMT, MECP2, NLGN4X, PAH, PEX7, POMGNT1, SYNE1 and VPS13B24. MECP2, NLGN4X and SYNE1 have been traditionally associated with ASD. A recent investigation employing CMA and WES by the Autism Genome Project (AGP) on 2,147 ASD patients found 4.6% (n = 99) carried a de novo rare CNV29. Studies by the Simons Simplex Collection prove the incidence of de novo rare CNVs ascends to over 10% when limited to simplex syndrome. Likewise, a study of 1,532 families with multiply-affected patients from the Autism Genetic Resource Exchange (AGRE) proved that both rare de novo and hereditary CNVs further ASD progression. And while the incidence of de novo CNVs discovered in the AGRE study as expected proved lower than the simplex cases, a higher burden of large, rare CNVs including hereditary deviations in ASD patients contrasted with their unafflicted siblings. Compellingly, in over two-thirds of the families in which a high-risk ASD-related CNV was identified, this CNV did not manifest in all afflicted siblings, underscoring the intrafamilial inherited heterogeneity of ASD.

[Autism Genetics Opportunities and Challenges for Clinical Translation]