



CIGNA MEDICAL COVERAGE POLICY

This Coverage Policy should NOT be used for Great-West benefit plans.

**Subject Autism Spectrum
Disorders/Pervasive
Developmental Disorders:
Assessment and Treatment**

**Effective Date 12/15/2008
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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

Coverage Policy

Some benefit plans specifically exclude therapy for learning disabilities, developmental delays, autism, and mental retardation or for that which is not restorative in nature. Please refer to the applicable benefit plan document to determine terms and conditions of coverage. Coverage for treatment of autism spectrum disorders (ASD) may also be mandated by state and/or federal mandates.

Services provided by a psychiatrist, psychologist or other behavioral health professionals may be subject to the provisions of the applicable behavioral health benefit.

Assessment and treatment for comorbid behavioral health and/or medical diagnoses and associated symptoms and/or conditions may be covered under applicable medical and behavioral health benefit plans.

When not otherwise excluded, CIGNA covers medically necessary services for the treatment of autism spectrum disorders (ASD) when the criteria of the Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition, Text Revision (DSM-IV-TR) are met.

Please refer to the CIGNA Coverage Policies on Speech/Language Therapy, Occupational Therapy and Physical Therapy for specific coverage criteria for these therapies.

CIGNA covers genetic testing for ASD as medically necessary for the following situations:

- for confirmation testing for FMR1 gene mutation when fragile X syndrome is suspected in the presence of either dysmorphic features or mental retardation
- for confirmation testing for MECP2 gene mutations when Rett's Disorder is suspected
- for carrier testing when there is a positive family history of fragile X syndrome or Rett's disorder in a first- or second-degree* relative and the couple has the capacity and intention to reproduce
- for prenatal or preimplantation genetic diagnosis (PGD) testing when either parent is a known carrier of a disease-causing mutation of genes FMR1 or MECP2.

Services that are considered primarily educational or training in nature or related to improving academic or work performance are not covered under many benefit plans. CIGNA does not cover the following services for the assessment and/or treatment of ASD because they are primarily educational and training in nature (this list may not be all- inclusive):

- education and achievement testing
- educational interventions (e.g., classroom environmental manipulation, academic skills training and parental training)

CIGNA does not cover the following procedures/services for the assessment and/or treatment of ASD because they are considered experimental, investigational or unproven for this indication (these lists may not be all-inclusive):

Assessment:

- allergy testing (e.g., food allergies for gluten, casein, candida, molds)
- celiac antibodies testing
- erythrocyte glutathione peroxidase studies
- event-related potentials (i.e., evoked potential studies)
- hair analysis
- immunologic or neurochemical abnormalities testing
- intestinal permeability studies
- magnetoencephalography (MEG)
- micronutrient testing (e.g., vitamin level)
- mitochondrial disorders testing (e.g., lactate and pyruvate)
- neuropsychological testing
- provocative chelation tests for mercury
- stool analysis
- urinary peptides testing

Treatment:

- auditory integration therapy
- augmentative communication devices
- chelation therapy

- cognitive behavioral therapy
- cognitive rehabilitation
- craniosacral therapy
- dietary and nutritional interventions (e.g., elimination diets, vitamins)
- facilitated communication
- holding therapy
- hyperbaric oxygen therapy
- immune globulin therapy
- intensive intervention programs for autism (e.g., early intensive behavior intervention [EIBI] intensive behavior intervention [IBI], Lovaas therapy, applied behavior analysis [ABA])
- music therapy
- secretin infusion
- sensory integration therapy
- vision therapy

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

CIGNA does not cover genetic screening for ASD in the general population because such screening is considered not medically necessary or of unproven benefit.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.

Note: Coverage of medications related to the treatment of ASD is subject to the pharmacy benefit portion of the applicable benefit plan.

General Background

The autism spectrum disorders (ASD) are a range of complex behavioral disorders that are also referred to as pervasive developmental disorders (PDD). The disorders range from the condition referred to as autism or autistic disorder to Asperger's syndrome. Two other disorders in the spectrum are Rett's disorder and childhood disintegrative disorder. When a child has symptoms of autistic disorder or Asperger's syndrome, but does not meet the specific criteria for either, the diagnosis is described as pervasive developmental disorder not otherwise specified (PDD-NOS), which is also referred to as atypical PDD or atypical autism. All of these disorders are characterized by varying degrees of impairment in communication skills, reciprocal social interactions, and restricted, repetitive and stereotyped patterns of speech, interests and behavior (National Institute of Mental Health [NIMH], 2004/2008). The autistic spectrum includes the following (Rapin, 1997):

- Autistic disorder: This condition is also referred to as classic autism and involves measurable deficits in:
 - social interactions
 - language, communication and play
 - deficits manifested as stereotypies (i.e., persistent repetition of words, posture or movement without meaning), perseveration and a narrow range of interests and activities
- Asperger's syndrome: This disorder is associated with no clinically significant delay in cognitive development, with impairment in social interactions and narrow range of interests, but with preserved speech fluency and without speech delay.
- Pervasive developmental disorder not otherwise specified: This disorder includes children with autistic behavior who do not meet criteria for other disorders in the autistic spectrum.

- Disintegrative disorder (Heller's syndrome): This disorder includes previously normal children with massive regression between ages two and ten, resulting in severe acquired autism, with loss of cognitive skills.
- Rett's disorder: This is a specific disorder limited to girls, with acquired microcephaly, infantile regression, lack of hand use, stereotypic hand movements, severe retardation and other neurologic problems.

In February 2007, the Centers for Disease Control and Prevention (CDC) published updated data regarding the prevalence of ASD. The CDC estimates that two to six per 1,000 or one in 150 children have an ASD. The risk is three to four times higher in males than in females. This is a higher rate than previous studies have indicated. The CDC notes that there is a debate regarding whether this represents a true increase in the prevalence. Contributing factors to this data may be changes in the criteria used to diagnose autism, along with increased recognition of the disorder by professionals and the public (CDC, 2007).

The precise etiology of autism is unknown, although there appears to be a strong genetic basis. This is a field of active research. In October 2006, the CDC initiated a multi-state collaborative study to help identify factors that may put children at risk for ASDs and other developmental disabilities. Approximately 2,700 children, aged two to five, will be part of the study. There will be six sites participating in the study—five are the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) Network, along with the CDC participating and including children from the metropolitan Atlanta, GA area. The study will take place over five years. It is anticipated that the study will provide information regarding the characteristics of children with ASDs, factors associated with developmental delays, and how genes and the environment may affect child development. The information will be obtained by conducting interviews and exams, reviewing medical records, collecting cheek swabs, and blood and hair sampling. In this study, referred to as the Study to Explore Early Development (SEED), a number of factors will be studied for their potential association with ASDs, including (CDC, 2006):

- infections or abnormal responses to infections in the child, mother or father
- genetic factors in the child, mother and father
- mother's reproductive history
- abnormal hormone function in the child, mother or father
- gastrointestinal problems in the child
- family history of medical and developmental problems
- smoking, alcohol and drug use in pregnancy
- parent's occupation and other socio-demographic factors

Associations between ASD and a number of medical conditions have been proposed. Several other disorders are associated with ASD. These include (National Institute of Child Health and Human Development [NICHD], 2005a):

- Epilepsy or seizure disorder: Nearly one-third of those with autism also show signs of a seizure disorder.
- Tuberous sclerosis: Approximately six percent of those with autism also have this rare multi-systemic, genetic disease that causes noncancerous tumors to grow in the brain and other vital organs. It may result in symptoms that include: seizures, developmental delay, behavioral problems, skin abnormalities and kidney disease.
- Fragile X syndrome: About 2.1% of those with autism also have this condition that is the most common inherited form of mental retardation.
- Mental retardation: Approximately 25% of persons with autism also have some degree of mental retardation.

Assessment

It has been suggested that early identification and initiation of early interventions results in improved management for most children with ASD. Routine developmental surveillance should be conducted by all providers at every well-child visit. Indications for immediate evaluation of ASD include (Filipek, et al., 2000):

- no babbling or pointing or other gesture by 12 months
- no single words by 16 months

- no two-word spontaneous (not echolalic) phrases by 24 months
- any loss of any language or social skills during the preadolescent years

The evaluation for ASD often requires a multidisciplinary team approach and will be dependent on the impairments that are present. The team may include a pediatrician, psychiatrist, psychologist, neurologist, speech therapist, occupational therapist, and social worker. There is no specific test that can confirm a diagnosis of ASD. The evaluation must include the following (Volkmar, et al., 1999; Tuchman, 2003; Filipek, et al., 2000):

- Clinical history: This includes parental report, family history, pregnancy, neonatal and developmental history of the child. Use of standardized questionnaires may be used.
- Clinical examination

The evaluation may include the following (Volkmar, et al., 1999; Tuchman, 2003; Filipek, et al., 2000):

- Audiologic evaluation
- Communication assessment performed by speech and language pathologist
- Assessment by occupational or physical therapist if there are motor deficits, motor planning or sensory dysfunction present
- Lead screening should be performed, particularly when pica is present
- Magnesium screening
- Cognitive assessment

There is consensus that the following tests are not needed for the evaluation of ASD; however, they may be considered appropriate for the evaluation of associated conditions:

- Chromosome tests may be performed to detect a syndromic condition such as fragile-X or other genetic etiology.
- Metabolic tests may be needed if the history or examination suggest.
- Neuroimaging studies are indicated only if the child is a candidate for specific interventions (e.g., epilepsy surgery).
- Electroencephalogram (EEG) may be performed if there is suspicion of a seizure.

The American Academy of Neurology (AAN) and Child Neurology Society (CNS) have developed evidenced-based practice parameters for the screening and diagnosis of autism. These parameters include the following developmental and assessment screening instruments that may be used in the evaluation process (Filipek, et al., 2000):

- The Ages and Stages Questionnaire
- The BRIGNACE[®] screens
- The Child Development Inventories
- The Parents' Evaluation of Developmental Status

The AAN/CNS practice parameters also note that screening for autism should be performed on all children failing routine developmental surveillance procedures and may include these tools (Filipek, et al., 2000):

- Checklist for Autism in Toddlers (CHAT): This test is used for children 18 months of age.
- Autism Screening Questionnaire: This test is used for children four years of age and older.

The AAN/CNS practice parameters noted that the Denver II (formerly the Denver Developmental Screening Test-Revised) is not recommended as a developmental screening tool for autism (Filipek, et al., 2000). It is also noted in the practice parameters that, "There is insufficient evidence to support the use of other tests such as hair analysis for trace elements, celiac antibodies, allergy testing (particularly food allergies for gluten, casein, candida and other molds), immunologic or neurochemical abnormalities, micronutrients such as vitamin levels, intestinal permeability studies, stool analysis, urinary peptides, mitochondrial disorders (including lactate and pyruvate), thyroid function tests, or erythrocyte glutathione peroxidase studies" (Filipek, et al., 2000). The practice parameters note that recording of event-related potentials and magnetoencephalography currently are

research tools and there does not appear to be evidence of routine clinical utility. There is insufficient evidence in the published peer-reviewed medical literature to support provocative chelation tests for mercury in the assessment of ASD.

Diagnostic criteria for 299.00 Autistic Disorder from:

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)

A. A total of six (or more) items from 1), 2), and 3), with at least two from 1) and one each from 2) and 3):

- 1) qualitative impairment in social interaction, as manifested by at least two of the following:
 - a) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
 - b) failure to develop peer relationships appropriate to developmental level
 - c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
 - d) lack of social or emotional reciprocity
- 2) qualitative impairments in communication as manifested by at least one of the following:
 - a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
 - b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
 - c) stereotyped and repetitive use of language or idiosyncratic language
 - d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
- 3) restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
 - a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 - b) apparently inflexible adherence to specific, nonfunctional routines or rituals
 - c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
 - d) persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age three years:

- 1) social interaction
- 2) language as used in social communication
- 3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Diagnostic criteria for 299.80 Rett's Disorder from:

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)

A. All of the following:

- 1) apparently normal prenatal and perinatal development
- 2) apparently normal psychomotor development through the first five months after birth
- 3) normal head circumference at birth

B. Onset of all of the following after the period of normal development:

- 1) deceleration of head growth between ages five and 48 months
- 2) loss of previously acquired purposeful hand skills between ages five and 30 months with the subsequent development of stereotyped hand movements (e.g., hand-wringing or hand washing)
- 3) loss of social engagement early in the course (although often social interaction develops later)

- 4) appearance of poorly coordinated gait or trunk movements
- 5) severely impaired expressive and receptive language development with severe psychomotor retardation

**Diagnostic criteria for 299.10 Childhood Disintegrative Disorder from:
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)**

- A. Apparently normal development for at least the first two years after birth as manifested by the presence of age-appropriate verbal and nonverbal communication, social relationships, play, and adaptive behavior.
- B. Clinically significant loss of previously acquired skills (before age 10 years) in at least two of the following areas:
 - 1) expressive or receptive language
 - 2) social skills or adaptive behavior
 - 3) bowel or bladder control
 - 4) play
 - 5) motor skills
- C. Abnormalities of functioning in at least two of the following areas:
 - 1) qualitative impairment in social interaction (e.g., impairment in nonverbal behaviors, failure to develop peer relationships, lack of social or emotional reciprocity)
 - 2) qualitative impairments in communication (e.g., delay or lack of spoken language, inability to initiate or sustain a conversation, stereotyped and repetitive use of language, lack of varied make-believe play)
 - 3) restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, including motor stereotypies and mannerisms
- D. The disturbance is not better accounted for by another specific Pervasive Developmental Disorder or by Schizophrenia.

**Diagnostic criteria for 299.80 Asperger's Disorder from:
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)**

- A. Qualitative impairment in social interaction, as manifested by at least two of the following:
 - 1) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression
 - 2) failure to develop peer relationships appropriate to developmental level
 - 3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
 - 4) lack of social or emotional reciprocity
- B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
 - 1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 - 2) apparently inflexible adherence to specific, nonfunctional routines or rituals
 - 3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
 - 4) persistent preoccupation with parts of objects
- C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.
- D. There is no clinically significant general delay in language (e.g., single words used by age two years, communicative phrases used by age three years).
- E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.
- F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia

This designation “not otherwise specified” (NOS) is used with pervasive developmental disorder (PDD-NOS) when the disorder appears to fall within the larger category but does not fully meet the criteria of any specific disorder within the above categories or does not have the degree of impairment described in the above four specific diagnoses.

Genetic Testing for Autism Spectrum Disorders (ASD)

The cause of autism is not known, but it appears that there may be a wide variety of genetic and non-genetic causes. This has been an area of ongoing research regarding autism as a genetic condition. It has been estimated that there is a sibling recurrence risk of approximately 5% (2–8%) (Freitag, 2007). Although it is thought that there is a genetic cause, the identity and number of genes involved remain unknown (Muhle, et al., 2004). Research indicates that there is no single biological or clinical marker for autism or that a single gene is responsible for the condition (Santangelo and Tsatsanis, 2005). The wide phenotypic variability of the ASDs is thought to be due to the interaction of multiple genes within an individual's genome and the existence of distinct genes and gene combinations among those affected (Muhle et al., 2004). The exception is Rett's disorder, where mutations in the MECP2 gene are thought to be responsible for the majority of cases with this condition.

Genetic testing for the majority of patients will have a very low yield unless the family history, medical history, presence of mental retardation, or dysmorphic or other findings on examination are suggestive of a diagnosable condition. Genetic counseling should assist in providing information to parents and children and estimate the recurrence risk. Conditions that may warrant genetic testing include situations where the results will directly impact clinical decision-making and/or clinical outcome, and the testing method is considered a proven method for the identification of a genetically-linked inheritable disease. The presence of dysmorphic features or other specific findings may suggest obtaining genetic screening for inherited metabolic disorders or chromosome analysis (Volkmar, et al., 1999). It may be appropriate to perform genetic testing in the following situations:

- Rett's disorder: This condition is one of the disorders in the autistic spectrum. Molecular testing for MECP2 mutations is clinically available. It is inherited in an X-linked dominant manner. It will usually result from either a de novo mutation in the child or inheritance of disease-causing mutation from one parent who has somatic or germline mosaicism (Christodoulou, 2006).
- Fragile X syndrome: This is the most common cause of inherited mental retardation and is due to a mutation on the X-linked FMR1 gene. Mutations of the FMR1 gene are responsible for over 98% of cases of fragile X (Sherman, et al., 2005). A small percentage of children with autism will have fragile X syndrome; however, approximately 50% of children with this syndrome have autistic behaviors (Miles and Mccathren, 2005).

Chromosomal microarray analysis (CMA) or comparative genomic hybridization (CGH) is a method that can identify small deletions and duplications of the subtelomeres, each pericentromeric region and other chromosome regions (Miles and Mccathren, 2005). It has been proposed that this testing be used in the genetic analysis of patients with ASD. There are few studies in the literature that examine the use of this testing. Jacquemont et al. (2006) reported on a case series where CMA was used in 29 patients with syndromic ASD. Eight clinically relevant rearrangements were identified in eight (27.5%) patients—six deletions and two duplications. No recurrent abnormality was identified. The authors in this study concluded that this testing should be considered in patients with ASD.

The American Academy of Pediatrics (AAP) guidelines for the identification and evaluation of children with ASD note that “comparative genomic hybridization-microarray analysis is a promising tool that may become standard of care in the future, but this technique has not been evaluated systematically in children with ASDs.” (Johnson, et al., 2007). The American College of Medical Genetics published practice guidelines for the clinical genetics evaluation in identifying the etiology of ASD (Schaefer, et al., 2008). The guidelines note that, “Currently, array comparative genomic hybridization (aCGH) has emerged as a powerful new tool that promises further revolution of clinical genetic testing. The technology of assessing submicroscopic rearrangements is evolving at a mind-boggling rate. New platforms are being developed at rates faster than clinical studies can define their use. The availability of multiple platforms further complicates the ability to compare studies from various sites. Relatively few studies have been published that provide an actual estimate of the diagnostic yield of aCGH in evaluating patients with autism.” The guidelines note that it can be estimated that current aCGH platforms can identify abnormalities on the order of 10% beyond what would be identified with standard chromosomal testing. They note that, “Until definitive, large-scale studies provide confirmation of the use of aCGH, its role in the evaluation of ASDs may not be fully appreciated.”

The clinical utility and the specific patients who are appropriate for CMA testing have not yet been determined. This testing method in all patients with ASD is still preliminary and is not yet recommended.

Treatment

There are no medical interventions that are effective in achieving a cure for autism; however, the condition may be managed through a combination of behavioral, pharmacological and educational interventions. The American Academy of Child & Adolescent Psychiatry (AACAP) practice parameters regarding assessment of children, adolescents and adults with autism and other pervasive developmental disorders note that treatments proposed should be based on solid, high-quality empirical evidence (Volkmar, et al., 1999). The AACAP guidelines note that educational services (e.g., including special education, some forms of behavior modification and other services) are the central and integral aspect of the treatment for ASD. Psychosocial interventions include parent training that involves behavior modification techniques and referral to support groups. It has been noted in the literature that there is no single approach that is best for all individuals with ASD.

Communication deficits are often present with ASD; however, speech pathology treatment is considered behavioral and training in nature. When these deficits overlap with an impairment of speech due to a separate neurological cause, speech therapy may be medically necessary.

Occupational and physical therapy may be needed to address specific fine or gross motor deficits or a comorbid physical impairment when there is potential for functional improvement.

Pharmacologic Treatment: Pharmacological treatments may be useful in the treatment of ASD. The AACAP guidelines note that, in general, the medications are not specific to autism and do not treat the core symptoms of the disorder; however, they may be useful for symptoms which interfere with participation in educational interventions or are a source of impairment or distress to the individual (Volkmar, et al., 1999). Pharmacologic intervention should be targeted toward specific behaviors that significantly interfere with daily functions (Filipek, et al., 2006). In October 2006, the U.S. Food and Drug Administration (FDA) approved Risperdal[®] (Janssen, L.P., Titusville, N.J.) (risperidone), an adult antipsychotic drug, for the symptomatic treatment of irritability in autistic children and adolescents. The FDA states that the approval is the first for the use of a drug to treat behaviors associated with autism in children. These behaviors are included under the general heading of irritability and include aggression, deliberate self-injury, and temper tantrums (FDA, 2006). The medications used in the treatment of ASD may include, but are not limited to, the following groups (NICHD, 2005a):

- Selective serotonin reuptake inhibitors (SSRIs): This is a group of antidepressants. They may be used to reduce the frequency and intensity of repetitive behaviors; decrease irritability, tantrums and aggressive behavior; and improve eye contact.
- Tricyclics and other antidepressants: Tricyclics tend to cause more side effects than the SSRIs; however, they may be more effective in certain individuals. Newer antidepressants that may be an alternative to tricyclics include, but may not be limited to, serotonin norepinephrine reuptake inhibitors (SNRIs).
- Antipsychotics: This group may be used to help control symptoms seen with ASD, including reducing self-injurious behaviors.
- Psychostimulants: This group of medications may be useful in increasing focus and decreasing hyperactivity in people with autism.
- Antianxiety drugs: This group can help relieve anxiety and panic disorders.

Secretin: Secretin has been proposed as a treatment for autism. Secretin is a hormone produced by the small intestine that assists in digestion. Secretin currently is approved by the U.S. Food and Drug Administration (FDA) for a single dose only for use in diagnosing digestive problems. The NIMH notes that anecdotal reports have noted improvement in autism symptoms; however, several clinical trials conducted in the last few years have found no significant improvements in symptoms between patients who received secretin and those who received a placebo (NIMH, 2004/2008). The AACAP issued a policy statement on the use of secretin in the treatment of autism and noted that the available evidence does not suggest that secretin is a useful treatment for autism, and use of this medication remains unproven (AACAP, 2002).

Sandler et al. (1999) conducted a double-blind placebo-controlled trial of a single dose of secretin in 60 children with ASD. The children were randomly assigned to receive a single intravenous infusion of secretin or a placebo

of saline. Fifty-six children completed the study. As compared with the placebo, secretin treatment was not associated with significant improvement in any of the outcome measures. The authors concluded that a single dose of secretin is not an effective treatment for ASD.

Levy et al. (2003) conducted a randomized, crossover, double-blind and placebo-controlled trial of a single intravenous dose of human synthetic secretin. The study involved 62 subjects. Sixty-one children completed the study. Compared with placebo, secretin treatment was not associated with significant improvement measured with the Communication and Symbolic Behavior Scale (CSBS). Five children showed clinical improvement in standard scores: two after the secretin and three after placebo. The authors concluded that a single dose of intravenous human secretin is not effective in changing behavior and communication in children with ASD when compared to placebo.

Williams et al. (2005) conducted a Cochrane review to determine if intravenous secretin: 1) improves the core features of autism (i.e., social interaction, communication and behavior problems); 2) improves the non-core aspects of behavior or function such as self-injurious behavior; 3) improves the quality of life of affected individuals and their caregivers; 4) has short-term and long-term effects on outcome; and 5) causes harm. Fourteen studies met inclusion criteria for this review. The review noted that outcomes were reported at between three and six weeks, and no outcome beyond six weeks was reported. It was noted that the review found no evidence that single or multiple doses of intravenous secretin is effective across a range of outcomes and concluded that secretin should not be currently recommended or administered as a treatment for ASD.

Toda et al. (2006) conducted a single-blind crossover study to evaluate the clinical effects of intravenously administered secretin in 12 children with autism. The children were ages four to six years, with eight boys and four girls. In addition to the association between improvement in symptoms, cerebrospinal fluid (CSF) was examined for changes in a metabolite of dopamine and metabolite of serotonin and a coenzyme. After administration of secretin, the Autism Diagnostic Interview-Revised (ADI-R) score improved in seven of the 12 children. Behaviors were evaluated before administration and two, four, six, and eight weeks after the administration. The score deteriorated in two of the 12 children. Elevation in the levels in CSF was noted with improvement in the ADI-R score. The authors theorized that these findings suggest that secretin activated metabolic turnover of dopamine in the central nervous system, thereby improving symptoms. They noted that, in the future, the detailed mechanism of this effect should be further investigated.

Auditory Integration Training (AIT): AIT refers to listening to music that has been computer-modified to remove frequencies to which an individual demonstrates hypersensitivities and to reduce the predictability of auditory patterns. A special device is used to modify the music for the treatment sessions. Auditory thresholds are determined via audiograms. The audiogram is then reviewed for evidence of hyperacusis (i.e., an abnormal sensitivity to sound). A clinical history of sound sensitivities and behavior is also reviewed. Audiograms are repeated midway and at the end of the training session to document progress and to determine whether further treatment sessions are necessary. AIT is usually provided by a speech-pathologist or audiologist. This treatment has been proposed for improving abnormal sound sensitivity in individuals with behavioral disorders, including autism spectrum disorders. Evidence supporting the use of this technique is limited, thus the role of AIT in the treatment of ASD has not been established.

A Cochrane review was conducted with the objective of determining the effectiveness of AIT or other methods of sound therapy in individuals with autism spectrum disorders (Sinha, et al., 2004). Six randomized controlled trials of AIT were identified, including one crossover trial. Four trials had fewer than 20 patients involved in the study. Seventeen different outcome measures were used. It was noted in the review that due to the high heterogeneity or presentation of data in unusable forms, a meta-analysis was not possible. It was noted that three studies did not demonstrate benefit of AIT over the control conditions. Three trials reported improvements at three months for the AIT group with the Aberrant Behavior Checklist (ABC), which is of questionable validity. The reviewers concluded, "Further research is needed to determine the effectiveness of sound therapies. In the absence of evidence, the treatment must be considered experimental and care must be taken not to risk hearing loss" (Sinha, et al., 2004).

Several professional organizations have determined that evidence is insufficient regarding the efficacy of AIT. The American Speech-Language-Hearing Association (ASHA) prepared an evidenced-based technical report regarding AIT treatment (ASHA, 2004). They noted that, despite approximately one decade of practice, this method has not met scientific standards for efficacy and safety that would justify its inclusion as a mainstream

treatment for a variety of communication, behavioral, emotional and learning disorders. The American Academy of Audiology (AAA) has published a position statement regarding AIT (AAA, 1993). The statement notes that, "that there are no published results of peer-reviewed studies using controlled populations and using scientific methods that demonstrated whether this auditory training program provides significant improvement in any dimension for any population." It is also noted that the organization believes this training to be entirely investigational, and further research is needed to demonstrate the efficacy. The Educational Audiology Association (EAA) issued a position statement regarding AIT (EAA, 1997). They stated that "Auditory integration therapy has not been proven to be a viable treatment for any disability. Only inconsistent, uncontrolled anecdotal evidence has been provided to support claims of changes in auditory performance." In addition, the position statement noted that without controls to protect against excessively loud auditory stimuli, AIT may cause harm to the auditory system. The AAP has published a statement regarding two treatments proposed for autism (i.e., AIT and facilitated communication) (AAP, 1998/2006). They have noted that as yet there are no good controlled studies to support the use of AIT for children with autism. It is also noted that until further information is available, the use of these treatments does not appear warranted at this time, except within research protocols.

An assessment by the National Research Council (NRC) Committee on educational intervention for children with autism concluded that there is insufficient evidence of the effectiveness of AIT for autism (NRC, 2001). A review of the scientific literature does not support the efficacy of AIT for the treatment of patients with ASD.

Augmentative Communication Devices: Augmentative communication devices may be provided in the educational setting as part of the management of ASD. The review by the NRC noted that "for children with autism who do not acquire functional speech or have difficulty processing and comprehending spoken language, augmentative and alternative communication (AAC) and assistive technology (AT) can be useful components of an educational program " (NRC, 2001). The NRC review also notes that, "there is relatively little rigorous, systematic research to elucidate characteristics of children and the components of AAC and AT that may interact to produce effective (or ineffective) intervention." AAC ranges from supporting existing speech or developing independent use of a nonverbal symbol system such as sign language, symbols displayed on a communication board and voice output devices with synthesized and digitized speech. AT is defined as a device or service that is commercial, hand-made, or customized and is used to support or enhance the functional capabilities of an individual with disabilities (NRC, 2001).

Millar et al. (2006) conducted a meta-analysis to determine the effect of AAC on the speech production of individuals with developmental disabilities. The review included 23 studies, involving 67 individuals. Of the 23 studies, eight were descriptive case studies; six were single-participant, alternating treatment designs; six were single-participant, multiple baseline designs; one was single-participant, alternating treatment design within a multiple baseline; one was a single-participant withdrawal design; and one was a group pretest, post-test design. Of the 67 participants, 40% had mental retardation, 31% had autism, and the rest had other disabilities. The goal of 70% of the studies was to teach expressive vocabulary, either in the form of single words or short phrases; the goal of the remaining studies was to teach expression of various communicative functions (e.g., requests, comments). Sixty-one percent of the studies investigated unaided interventions (e.g., manual signs); 31% investigated nonelectronic aided AAC systems; one study investigated a combination AAC system with speech output and aided AAC system without speech output; and one study investigated multimodal interventions combining unaided and aided AACs without speech output. It was noted that six of the 23 studies had sufficient methodological rigor to support conclusions regarding the effect of AAC on speech production. These six studies involved 27 cases (i.e., 17 participants who may have participated in more than one treatment condition). In addition, variation in the participants, speech production and intelligibility were not clearly defined in most studies. None of the 27 cases demonstrated a decrease in speech production as a result of AAC intervention; 11% showed no change; and 89% demonstrated gains in speech. It was noted that for most of the cases, gains were modest. The authors concluded that future research is needed to better delineate the relationship between AAC intervention and speech production across a wide range of participants and AAC interventions.

Chelation Therapy: Chelation has been proposed for treatment of ASD. The proposal is based on the theory that the chelating agent will remove mercury that is thought to be contained in the tissue after early childhood vaccinations in children with ASD (Levy and Hyman, 2005). While there have been several studies that have examined the relationship of mercury to ASD, no consistent associations have been identified (Levy and

Hyman, 2005). A review of the published, peer-reviewed literature indicates that there are no studies regarding the efficacy of chelation therapy for treatment of ASD.

Cognitive Behavioral Therapy: Cognitive behavioral therapy is based on the theory that psychological or behavioral problems are a result of cognitive deficiencies and cognitive distortions. The aim of the therapy is to identify and correct these deficiencies and distortions of thinking patterns, in order to alleviate the psychological or behavioral problem. The Wessex Institute for Health Research and Development conducted a review of the literature regarding cognitive behavioral therapy for ASD. The review found evidence that some children experienced improvement in coping strategies for anxiety- promoting situations, behavior and social interaction after this therapy; however, the lack of reliable controlled studies makes it impossible to attribute these effects to cognitive behavioral therapy, or to compare effects of this treatment with other interventions (White, 2004). There is insufficient evidence in the published, peer-reviewed medical literature to support the use of cognitive behavioral therapy for ASD.

Cognitive Rehabilitation: Cognitive rehabilitation has been proposed as an intervention for ASD. This therapy involves a systematic, goal-oriented treatment program designed to improve cognitive functions and functional abilities, and increase levels of self-management and independence following neurological damage to the central nervous system. It is primarily used in rehabilitation of traumatic brain injury and stroke. There is insufficient evidence in the published medical literature to support the use of cognitive rehabilitation for ASD.

Craniosacral Therapy: Craniosacral therapy is a form of massage that involves using gentle pressure on the plates of the patient's skull. It is considered a complementary and alternative medicine (CAM) intervention. A review of the literature indicates that there is no evidence supporting the efficacy of this treatment for ASD and it would be considered unproven.

Dietary and Nutritional Interventions: Various dietary interventions involving elimination diets, nutritional supplements and vitamins have been proposed for treatment of ASD. These include gluten and casein-free diets, a ketogenic diet, and providing diet supplements with vitamin B6 and magnesium (B6-Mg). There is insufficient evidence in the published, peer-reviewed medical literature to support the use of dietary and nutritional interventions in the management of ASD.

The proposal of a gluten and/or casein-free diet is based on the thought that the peptides from gluten and casein may have a role in the physiology of autism and that a diet free from these substances may reduce the symptoms associated with the condition. Millward et al. (2004) conducted a Cochrane review to examine the effectiveness of gluten and/or casein-free diets on symptoms of individuals with ASD. Only one trial met inclusion criteria. This trial was a small, single-blinded trial of combined gluten and casein-free diet versus a normal diet. It was noted that three of the four outcomes (i.e., cognitive skills, linguistic ability and motor ability) that were reported on were not significant; however, the fourth outcome, reduction in autistic traits did show a significant beneficial treatment effect for the combined gluten and casein-free diet. The authors concluded that, "Though the results of one small trial adds weight to the existing anecdotal evidence for a gluten and/or casein-free diet for autism, there is not yet sufficient evidence for clinicians to advise the use of such diets in cases of autistic spectrum disorder" (Millward, et al., 2004). In 2008, an update to the 2004 Cochrane review was published (Millward, et al., 2008). A second study was identified and included in the review—a small pilot, randomized, crossover trial with 15 children. There was not sufficient homogeneity of outcomes to perform a meta-analysis. In the second study there was no significant difference between the diet and control group for outcomes which were reported on the Childhood Autism Rating Scale (CARS). The authors note the second trial did appear to be well-designed and provides a blueprint for future studies in this area.

Another dietary intervention, the use of ketogenic diets, has also been proposed. A review of the literature identified only one study regarding this intervention (Erickson, et al., 2005). In this study, 30 autistic children, all concurrently taking haloperidol, were placed on a ketogenic diet. The study found that 60% of the children tolerated the diet and, within this group, improvement was noted on the Childhood Autism Rating Scale, with the less severely impaired children showing more improvement. Since the study lacked a control group, it is difficult to interpret the results.

Interventions utilizing vitamin B6 and magnesium (B6-Mg) have been proposed. A Cochrane review was conducted to determine the efficacy of B6-Mg to treat the social, communication, and behavioral responses of children and adults with ASD (Nye and Brice, 2005). Nineteen studies were identified; however, only three

studies were included in the review. The three studies each included a small number of participants. The reviewers concluded that due to the small number of studies, the methodological quality of studies, and the small sample size, no recommendation can be made regarding the use of B6-Mg as a treatment for autism. The review noted that there is insufficient evidence to demonstrate treatment efficacy.

Facilitated Communication (FC): This treatment is a method of providing assistance to a nonverbal person in typing out words using a typewriter, computer keyboard, or other communication device. FC involves supporting the individual's hand to make it easier for him or her to indicate the letters that are chosen sequentially to develop the communicative statement. Proponents claim that this manual prompting by a trained facilitator provides expressive language abilities in a wide range of individuals, including those with severe intellectual disabilities or autism. FC has been at the center of a growing controversy, because several scientific studies have suggested that facilitators may unintentionally influence the communication, perhaps to the extent of actually selecting the words themselves. A review of the scientific literature has shown many controlled studies with consistently negative findings, indicating that the technique is neither reliably replicable nor valid.

Several professional organizations have published statements regarding FC that indicates this treatment is unproven. The AAP has published a statement regarding two treatments proposed for autism: AIT and facilitated communication. According to the AAP, there is good scientific data showing FC to be ineffective; therefore, its use does not appear warranted at this time (AAP, 1998/2006). The AACAP published a policy statement regarding facilitated communication that states, "Studies have repeatedly demonstrated that FC is not a scientifically valid technique for individuals with autism or mental retardation. In particular, information obtained via (FC) should not be used to confirm or deny allegations of abuse or to make diagnostic or treatment decisions" (AACAP, 1993/2008). The American Psychological Association (APA) has adopted the position that facilitated communication is a controversial and unproven communicative procedure with no scientifically demonstrated support for its efficacy (APA, 1994). A review of the scientific literature does not support the efficacy of FC for the treatment of patients with ASD.

Holding therapy: In this intervention the therapist or parent holds the child until they stops resisting or until a fixed amount of time has elapsed. Those who support the technique maintain that it forges a bond between the parent or therapist and child. The effectiveness of this therapy has not been demonstrated in the published peer-reviewed scientific literature.

Hyperbaric Oxygen Therapy: Hyperbaric oxygen therapy (HBO or HBOT) is a mode of treatment in which a patient breathes 100% oxygen at pressures greater than normal atmospheric (sea level) pressure. This treatment has been proposed as a treatment for ASD. Rossignol and Rossignol (2006) reported on a retrospective case series of 6 children, aged 2 to 7 years, diagnosed with autism and treated with low-pressure hyperbaric oxygenation. The patients received treatment 40 1-hour sessions of HBOT at 1.3 atmospheres absolute and 28% to 30% oxygen. One patient completed only 25 sessions but was included in the analysis. Three parent-reported behavior evaluation instruments were used to measure outcomes. Modest improvement was noted in all scoring systems, with greater changes recorded for the younger children. The authors theorized that HBOT may permanently improve behavioral symptoms in these patients.

Rossignol et al. (2007) reported on a prospective study of 18 children with autism who were treated with HBOT at atmospheric pressures and oxygen concentrations to determine the effects of HBOT on oxidative stress markers before and after the treatment and to determine the impact of HBOT on an inflammatory marker (C-reactive protein). The children underwent 40 hyperbaric sessions of 45 minutes duration at either 1.5 atmospheres (atm) and 100% oxygen, or at 1.3 atm and 24% oxygen. Neither group showed statistically significant changes in mean plasma GSSG levels, which appeared to indicate that intracellular oxidative stress appears unaffected by either regimen. There was a trend towards improvement in mean CRP noted in both groups. The largest improvements were observed in children with initially higher elevations in CRP. When all 18 children were pooled, a significant improvement in CRP was noted ($p= 0.021$). Pre- and post-parental observations indicated statistically significant improvements in both groups, including motivation, speech, and cognitive awareness ($p < 0.05$).

Data provided by these studies is preliminary and is insufficient to support HBO as a treatment for ASD.

Immune Globulin: Intravenous immunoglobulin (IVIG) has been proposed and administered to children with ASD. It is based on the theory that an immune deficiency may exist in ASD. A review of the literature by Levy

and Hyman (2005) indicates that there are three small-case series published regarding this treatment. All three studies had a small number of participants and did not demonstrate the efficacy of this treatment. The AAP's technical report on the pediatrician's role in the diagnosis and management of ASD notes that larger controlled investigations would be needed to assess this kind of treatment; however, there is no scientific evidence to justify the use of infusions of immune globulin to treat children with ASD (AAP, 2001). The published literature does not demonstrate the efficacy of IVIG for treatment of ASD.

Intensive Intervention Programs: The start of these programs was in the 1980s, as researchers began to report positive outcomes of early intensive behavior intervention programs, including increases in developmental levels, gains in intelligence quotient (IQ) scores, improvements in social behavior, and decreases in signs of autism. These programs incorporated behavior modification and applied behavior analysis. Behavior analysis is a behavioral assessment of the child and environmental conditions that may be used to help the child develop higher skills through behavioral procedures. These methods are based on research in the application of learning principles to the education of autistic children and incorporate behavior modification, training and education. Procedures that strengthen desired behaviors and/or decrease undesirable behaviors are used as part of an individualized intervention plan (Volkmar, et al., 1999). These programs are increasingly prescribed by school systems as an intervention that is part of the individualized educational plan (IEP). In younger children these treatments may also be provided in the home. The programs are frequently referred to as early intensive behavior intervention (EIBI). EIBI focuses on identifying behaviors that interfere with normal developmental processes, understanding the relationship between a behavior and the child's environment and modifying those behaviors in such a way so as to improve the child's functional capacity. EIBI may also be referred to as intensive behavior intervention (IBI) or early intensive behavioral treatment (EIBT). At times, the terms EIBI, IBI, EIBT are used interchangeably with applied behavior analysis (ABA), Lovaas therapy or Lovaas University of California Los Angeles (UCLA) Program. The Lovaas Model of Applied Behavior Analysis is a form of ABA initially started at UCLA and currently provided at various Lovaas clinics.

Intensive intervention programs other than those that focus on behavior analytic treatment have also emerged in recent years. The TEACCH program (Treatment and Education of Autistic and Related Communication Handicapped Children) has been implemented in many special education programs for autistic children, and includes behavioral analytic approaches for some skills but uses other interventions as well. The focus of the Colorado Health Sciences program (Denver Model) is learning through play based on Piaget and object relations theories. Behavior analytic techniques are included for behavior management. The Rutgers program is a home-based, early-intensive, behavioral intervention program with similarities to the Lovaas program. Families are trained in the program and provide the treatment or hire staff trained in the program. The Learning Experiences and Alternative Program (LEAP) includes both a preschool program and a behavioral skill training program for parents, as well as national outreach activities. The program includes an individualized curriculum that targets goals in social, emotional, language, adaptive behavior, cognitive, and physical developmental areas (NRC, 2001).

Literature Review for Intensive Intervention Programs: Lovaas therapy is based on a prospective, quasi-randomized trial published by O. Ivar Lovaas in 1987. In the University of California, Los Angeles (UCLA) Young Autism Project, subjects were assigned to an intensive-treatment experimental group (n=19) or control group (n=19). Outcome measures were limited to IQ and school placement. Student therapists trained in the technique provided more than 40 hours of one-on-one treatment per week in the home, school or community for two or more years to those assigned to the experimental group. Parents received extensive training in the treatment procedures and worked as part of the treatment team to ensure that treatment continued during most of the child's waking hours. The primary teaching method relied on discrete trial discrimination learning and compliance with simple commands. Aggressive and self-stimulatory behaviors were ignored and appropriate behaviors were reinforced. In some cases physical punishment (slap on the thigh) or verbal reprimands (a loud "No!") were used to decrease inappropriate behavior.

Children in the minimal treatment group received up to 10 hours per week of one-on-one behavioral treatment combined with special education. A second control group was created by selecting 21 children from a larger group (62) of young autistic children treated at another facility. These participants were never referred to or evaluated by the Lovaas team. Data from this control group were included in the study to guard against the possibility that subjects referred to the UCLA study were likely to have more or less favorable outcomes. The mean age and sex of participants in the second control group were not reported, nor were details on the specific treatment provided. The lack of random assignment to experimental or control groups and the fact that subjects

were assigned based on proximity to the UCLA campus and on staff availability raises the possibility of selection bias.

The UCLA Lovaas study reported that 47% of those in the intensive treatment group achieved normal intellectual and educational functioning, with normal IQ scores and successful first-grade performance in public schools. Another 42% were reported as mildly retarded and assigned to classes for the language delayed, and only 10% were deemed profoundly retarded and assigned to classes for the autistic/retarded. No children in the minimal-treatment control group and only one of 21 in the second control group (5%) achieved normal educational and intellectual functioning. A total of 45% were reported as mildly retarded and placed in language-delayed classes, and 53% were severely retarded and placed in autistic/retarded classes. Based on the results of this study, the researchers felt that Lovaas therapy was an effective treatment option for children with autism. A follow-up study (McEachin, et al., 1993) was conducted to assess the long-term effects of therapy provided in the Lovaas trial and concluded that long-lasting and significant gains could be made with early intensive behavioral treatment.

There were a number of methodological flaws in the Lovaas and McEachin studies, including:

- very small sample size
- group assignment based on staff availability, not truly randomized
- sample not representative of autism population (higher level of functioning, children on medications excluded, ratio of males to females not representative of that in population)
- autism subset classification of subjects not available
- different IQ tests used for different children at intake (examiner selection)
- social functioning not assessed after treatment; no outcome measures other than IQ scores and school placement

Sheinkopf and Siegel (1998) conducted a small (n=22) prospective, case-matched controlled trial which partially replicated the UCLA project. Children received less intensive treatment, an average of 18 to 25 hours/week, and providers received less supervision from senior staff. Children in the intensively treated group (n=11) scored an average of 28 points higher post-treatment than those in the control group (n=11). The study suggested that treatment need not be as intensive as that provided in the UCLA Lovaas study to be effective. Definite conclusions could not be made, however, because of the small sample size.

Several school-based studies, including LEAP (Learning Experiences: an Alternative Program), and the Princeton Child Development Institute (PCDI) program, were conducted using intensive behavioral therapy during the 1980s and early 1990s, yielding inconsistent results. Improvements were reported, but the nature of the improvements varied significantly across studies. No clear correlation could be made between treatment intensity, treatment model and outcome (Smith, 1999). All of these studies contained many methodological weaknesses, including small numbers of patients and a lack of a procedure to randomly assign participants to groups. Participants were diagnosed as autistic by independent clinicians, but in most of these studies a standardized diagnostic tool, the Childhood Autism Rating Scale (CARS), was not used. Some children may not have met generally accepted autism diagnostic criteria.

Sallows and Graupner (2005) reported on a study of children with autism that were randomly assigned to a clinic-directed group, replicating the parameters of the early intensive behavioral treatment developed at UCLA, or to a parent-directed group that received intensive hours but less supervision by equally well-trained supervisors (Wisconsin Early Autism Project [Madison]). Twenty-three children were assigned to either clinic-directed group (n=13) replicating parameters of the UCLA intensive behavioral treatment or to the parent-directed group (n=10), which was intended to be a less intensive treatment. Children in the clinic group received an average of 39 hours of direct treatment in the first year and 37 in the second year with gradual decrease in hours as children entered school. The average for the parent-directed group was 32 hour in first year, 31 in the second year with one family choosing to receive 14 hours both years. Among the 23 children, the average Full Scale IQ increased from 51 to 76. After one year of treatment eight of the children reached IQ of 85 or higher, (five clinic-directed and three parent directed) and three children reached this level after three to four years of treatment (three parent-directed) which was a total of 11 or 48% of the children. It was noted that children with higher pre-treatment IQs were more likely to reach four year IQs in the average range. It was noted that these children also demonstrated increases in language and adaptive areas —succeeding in regular first or second

grade classes, demonstrating generally average academic abilities, spoke fluently and had peers with whom they played regularly. The parent-directed children did approximately as well as the clinic-directed children which was unexpected. It was noted that low IQ (below 44) and absence of language (no words of 36 months) predicted limited progress. It is planned that these children will be followed for several more years to determine outcome in adolescence and adulthood.

Howard et al. (2005) studied the effects of three treatment approaches on preschool-age children with ASD. Intensive behavior analytic intervention (IBT) with a 1:1 adult: child ratio at 25–40 hours a week was provided to 29 children in community, home and school setting. Intensive “eclectic” intervention, which was a combination of methods (combination of TEACCH, sensory integration therapy and some applied analysis methods) with a 1:1 or 1:2 ratio, at 30 hours a week was provided to a comparison group (n=16) in public special education classrooms (AP group). A second comparison group (GP) (n=16) in a non-intensive public early intervention programs received a combination of methods, provided in small groups, at 15 hours per week. Standardized tests of cognitive, language and adaptive skills to children were administered at intake and approximately 14 months after treatment began. At intake the groups were similar on key variables. It was noted that at follow-up, there did not appear to be statistically significant differences between the mean scores of children in the AP and GP groups. The IBT group had higher mean scores in all domains than the AP and GP groups that appeared to be statistically significant. An exception to this general finding was in the motor skills domain, which did not produce a statistically significant group difference when results were expressed as learning rates. At follow-up, the IBT group had mean standard scores in the normal range on cognitive, non-verbal, communication, and motor skills, whereas the only mean score in the normal range for the AP and GP groups was in motor skills. Limitations of the study included: assignment was parent-determined, not random; the examiners who performed the assessments were not blind as to the group assignments at follow-up testing; results were analyzed in terms of performances on standardized, norm-referenced assessments conducted in formal testing situations, rather than repeated direct observational measurement of behavior in situ that characterized applied behavior analysis.

Remington et al. (2007) reported on a study of preschool children with autism treated either with early intensive behavioral intervention or treatment as usual. Children in the intervention group (n=23), that were identified on the basis of parent preference, received home-based early intensive behavioral intervention for two years. One-to-one teaching based on applied behavior analysis for 25.6 hours per week on average was delivered by trained tutors and parents. The comparison group (n=22) received their local education authorities' standard provision for young children with autism—a variety of interventions designed to ameliorate the impact of autism and enhance functioning, none of which were intensive or delivered on one-to-one basis for most of the time. Prospective assessment was performed before treatment, after 1 year of treatment, and again after 2 years. Norm-referenced instruments were used to gather the cognitive, language, and behavioral outcome data. The measurements included: Bayley scales and Standard Binet Intelligence Scale: fourth edition was used for intellectual functioning. The Reynell developmental language-scales-third edition was utilized for language assessment. Adaptive skills were measured with the Vineland Adaptive Behavior Scale-Survey Form. In the area of child behavior the Positive Social subscale of the Nisonger Child Behavior Rating form along with the parent report versions of the Developmental Behavior Checklist were used. For IQ, there was a significant main effect of group (p=.008), but no interaction effect. Significant group effects (but no interactions) were also found for Vineland Daily Living Skills (p=.016), and Vineland Motor Skills (p=.040), but not for the Vineland Composite score or the Socialization and Communication domains. In all cases, the children receiving early intensive behavioral intervention appeared to out-perform the children in the comparison group. At baseline assessments the groups did not differ, but after 2 years, it was noted that there were strong differences that favored the intensive behavioral intervention in areas of intelligence, language, daily living skills, positive social behavior, and a statistical measure of best outcome for individual children.

Ben-Itzhak and Zachor (2007) reported on a study that assessed the relation between pre-intervention variables including cognition, socialization and communication, to outcome in young children with autism. The study included 25 children with autism who were enrolled in intensive behavior intervention. The children attended a center-based ABA program. A trained behavior analyst planned and supervised the individual intervention curriculum of each child and the treatment was provided one-on-one by skilled behavioral therapists for at least 35 weekly hours. The treatment included parents taught how to use behavioral methods at home and working with the program supervisor on developmental goals for use in natural environments. The children were separated into groups based on IQ scores and on the severity of social interaction and communication deficits. Six developmental-behavioral domains were assessed at pre- and post-one year of intervention times. The

domains included imitation, receptive language, expressive language, nonverbal communication skills, play skills and stereotyped behaviors. After one year of intervention, significant progress was noted in all the six developmental-behavioral domains. Children with higher initial cognitive levels and children with fewer measured early social interaction deficits demonstrated an increased acquisition of skills in three developmental areas, receptive language expressive language and play skills. Better progress in receptive language skills was seen in both groups. Improved progress in expressive language was associated with the child's social abilities, while more significant progress in play skills was related to pre-intervention cognitive level.

Magiati et al. (2007) conducted a prospective study to compare outcome for pre-school children with ASD receiving autism-specific nursery provision or home-based EIBI in a community setting. The study included 44 children, (aged 23- to 53-months) with ASD. Twenty-eight children were in EIBI home-based programs and 16 in autism-specific school based nursery provision which included a minimum of 15 hours per week. Cognitive, language, play, adaptive behavior skills and severity of autism were assessed initially and two years later. Improvements were noted in both groups in age equivalent scores but standard scores changed little over time. At follow-up, no significant group differences were noted in cognitive ability, language, play or severity of autism. The only difference approaching significance ($p=.06$), in favor of the EIBI group, was for Vineland Daily Living Skills standard scores. There were large individual differences in progress, with intake IQ and language level best predicting overall progress.

Eikeseth et al. (2007) reported on outcomes for children who began intensive behavioral treatment between ages four and seven (mean age of 5.5 years). The children were assigned to either a behavioral treatment ($n=13$) or eclectic treatment ($n=11$ boys) based on staff availability. Children in both groups received treatment for a minimum of 20 hours a week from trained therapists at their local schools. The children in the behavioral group received ABA and the children remained in education programs that combined a variety of interventions (e.g., ABA, TEACCH, sensory integration and other approaches). In 2007, results were reported when the children had mean age of eight years, two months and follow-up was 31.4 months in the behavioral group and 33.3 in the eclectic group. When the children entered school the hours were reduced to a mean of 18 hours for the behavioral group and 16 hours for the eclectic group. The behavioral treatment group showed larger increases in IQ and adaptive functioning than did the eclectic group ($p<.05$). The behavioral treatment group also displayed fewer aberrant behaviors and social problems at follow-up. The largest gain was noted in IQ. The behavioral treatment group showed an increase of 25 points (from 62 to 87) as compared to 7 points (from 65 to 72) in the eclectic treatment group. Gains on the Vineland Adaptive Behavior Scales ranged from 9 points for Daily Living Skills to 20 points for Communication; in contrast, mean scores in the eclectic treatment group declined 6 to 12 points. Limitations of the study included that it was quasirandom rather than random group assignment, small sample size, and no direct quality control measures of treatment. Replications of the study are needed.

Reichow and Wolery (2008) conducted a comprehensive synthesis of early intensive behavioral interventions for young children with autism based on the UCLA Young Autism Project Model. The synthesis was comprised of three components: descriptive analyses; effect size analyses; and a meta-analysis. The review included data from 14 samples from 13 research reports. The selection of studies for this review involved seven inclusion criteria: study specified the EIBI was based on the UCLA model based on a replication of Lovaas; participants had diagnoses of autistic disorder, ASD, PDD, PDD-NOS; participants had a mean chronological age less than 84 months at the beginning of treatment; mean duration of EIBI was greater than or equal to 12 months; at least one child outcome measure was reported; experimental research designs (e.g., pre-test/post-test multiple-group design) or quasi-experimental research designs (i.e., nonequivalent control group design, one-group pre-test/post-test design) were used and (g) publication in English in a peer-reviewed journal. The mean effect size was 0.69 ($p<0.001$) which took into account effect sizes for IQ, adaptive behavior, expressive language, and receptive language. There were more samples (12 of 14) that had sufficient data to calculate the effect sizes for IQ than for the other measures. Limitations of the review included that the inclusion criteria were narrow. In addition the studies included limitations such as: participants were not selected randomly, they were not assigned randomly to groups, study sizes were small, narrow and questionable measures were used and treatment fidelity data were not reported.

Professional Societies/Organizations for Intensive Intervention Programs: The Alberta Heritage Foundation for Medical Research (AHFMR) published a technology assessment of intensive intervention programs based on reviews by the British Columbia Office of Health Technology Assessment (BCOHT), Emergency Care Research Institution (ECRI), and a review of 12 peer-reviewed outcome studies published by

Tristram Smith (Ludwig and Harstall, 2001). The assessment evaluated Lovaas therapy, TEACCH, the Rutgers Program, the Denver Program and the LEAP Program, and concluded that there is insufficient evidence to establish a relationship between the intensity and duration of any intensive intervention treatment program and outcome measures, such as intelligence tests, language development and adaptive behavior tests. The assessment noted that, "Because of the methodological limitations and weaknesses of existing research, evidence remains limited on the efficacy and effectiveness of one intervention in comparison to another. It does appear that children improve in functioning (as measured by various indices) with behavioural intervention programs. However, it remains to be determined if any one program is more effective than another program."

The assessment by the NRC on educational intervention for children with autism included a review of comprehensive programs for the treatment of ASD (NRC, 2001). They note that although there are limitations in outcome research, it is likely that many children benefit substantially from the programs. They include a review of ten model programs in their report, but note that not all existing programs are included. The report notes that "while substantial evidence exists that treatments can reach short-term specific goals in many areas, gaps remain in addressing larger questions of the relationships between particular techniques, child characteristics, and outcomes."

A New Zealand Health Technology Assessment (NZHTA) reviewed "the most recent and best evidence" for the effectiveness of behavioral and skill-based early intervention in the treatment of young children with Autism Spectrum Disorder (Doughty, 2004). The NZHTA determined that the majority of recent primary studies reviewed documented some improvement associated with the intervention; however, it remains to be determined whether any specific early and/or intensive intervention program is more effective than others. The included studies covered a range of interventions, and it was not clear that the definition of intensive behavioral treatment, parent training, or parent-managed behavioral therapy were uniform across studies. Details regarding intensity and duration of interventions were not documented in all studies, and most sample sizes were small. The NZHTA concluded that, given these and other limitations, the primary studies provide only very preliminary evidence regarding the effectiveness of behavioral and skill-based early interventions, and that further research with larger sample sizes from multi-site collaborations using identical methods and outcome measures is needed.

Scottish Intercollegiate Guidelines Network (SIGN) published evidenced-based clinical guidelines for the assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders (SIGN, 2007). Regarding intensive behavioral programs they note that most intensive behavioral programs for ASD are based on principles of behavior modification using ABA. The programs are intensive, usually involving 20-140 hours or intervention per week. The most well known is the Lovaas program. The recommendation is that the Lovaas program should not be presented as an intervention that will lead to normal functioning. They report did recommend "behavioural interventions be considered to address a wide range of specific behaviors in children and young people with ASD, both to reduce symptom frequency and severity and to increase the development of adaptive skills."

A clinical report for the management of children with ASD was published by the AAP published (Myers, et al., 2007). The report notes that, "Educational interventions, including behavioral strategies and habilitative therapies, are the cornerstones of management of ASDs. These interventions address communication, social skills, daily-living skills, play and leisure skills, academic achievement, and maladaptive behaviors." The AAP report notes that these programs may differ in philosophy and relative emphasis on particular strategies. The early childhood educational programs share many common goals. There is an increasing consensus that important principles and components of effective early childhood intervention for children with ASDs include the following (Myers, et al., 2007):

- An entry into intervention as soon as an ASD diagnosis is seriously considered rather than deferring until a definitive diagnosis is made
- A provision of intensive intervention, with active engagement of the child at least 25 hours per week, 12 months per year, in systematically planned, developmentally appropriate educational activities designed to address identified objectives
- A low student-to-teacher ratio to allow sufficient amounts of one-to-one time and small-group instruction to meet specific individualized goals
- An inclusion of a family component, including parent training as indicated

- A promotion of opportunities for interaction with typically developing peers to the extent that these opportunities are helpful in addressing specified educational goals
- An ongoing measurement and documentation of the individual child's progress toward educational objectives, resulting in adjustments in programming when indicated
- An incorporation of a high degree of structure through elements such as predictable routine, visual activity schedules, and clear physical boundaries to minimize distractions
- An implementation of strategies to apply learned skills to new environments and situations (generalization) and to maintain functional use of these skills
- The use of assessment-based curricula that address the following:
 - functional, spontaneous communication
 - social skills, including joint attention, imitation, reciprocal interaction, initiation, and self-management
 - functional adaptive skills that prepare the child for increased responsibility and independence
 - reduction of disruptive or maladaptive behavior by using empirically supported strategies, including functional assessment
 - cognitive skills, such as symbolic play and perspective taking
 - traditional readiness skills and academic skills as developmentally indicated

In regard to the efficacy of education interventions, the AAP report notes that the treatment “should be based on sound theoretical constructs, rigorous methodologies, and empirical studies of efficacy. Proponents of behavior analytic approaches have been the most active in using scientific methods to evaluate their work, and most studies of comprehensive treatment programs that meet minimal scientific standards involve treatment of preschoolers using behavioral approaches. However, there is still a need for additional research, including large controlled studies with randomization and assessment of treatment fidelity. Empirical scientific support for developmental models and other interventions is more limited, and well-controlled systematic studies of efficacy are needed.” (Myers, et al., 2007).

There is insufficient evidence in the published medical literature to demonstrate the long-term effectiveness and impact on health outcomes of intensive early intervention programs for children with autism. The effectiveness of specific intervention strategies, the duration and intensity of the interventions and the characteristics of children who respond have not been established.

Music Therapy: Music Therapy has been proposed as an intervention for ASD in an attempt to improve coordination and communication skills. The methods can vary and may involve the therapist musically responding to the child’s sounds and movements, singing a running commentary to the child’s actions, using play routines or stories set to music, or songs involving imitation (Ball, 2004). A review done by the Wessex Institute of Health Research and Development (Ball, 2004) noted that children with ASD may demonstrate slight improvement in speech and imitation during music therapy sessions, but the clinical importance of these changes may be negligible. The review also noted that the impact on behavior or social interaction outside the sessions is unclear, as are any long-term effects. The report concluded that there was insufficient evidence regarding the effects of music therapy on behavior in children with ASD.

Gold et al. (2006) conducted a Cochrane review to evaluate the effects of music therapy for individuals with autistic spectrum disorders. Three small studies (n=24) were included in the review. The studies examined the short-term effect of brief music therapy interventions (daily sessions over one week) for children with autism. Music therapy was superior to placebo therapy with respect to verbal and gestural communications skills. The effect on behavioral problems was not significant. The authors concluded that the studies were of limited applicability to clinical practice; the findings indicate that music therapy may help children with ASD to improve their communicative skills and that further research is needed to examine whether the effects of music therapy are enduring and to investigate the effects of music therapy in typical clinical practice.

Sensory Integration Treatment: Sensory integration treatment (SIT) has been proposed as a treatment for ASD. This treatment has been proposed as a method to improve the way the brain processes and organizes external stimuli, such as touch, movement, body awareness, sight and sound. The therapy is usually performed by occupational or physical therapists. Dawson and Watling (2000) conducted a systematic review of the research regarding the effectiveness of interventions for sensory and motor abnormalities in autism. Four studies on the effectiveness of sensory integration therapy in autism that utilized objective measures of behavior

to assess outcome were found. All but one had a sample size of fewer than six subjects. None of the studies had a comparison group. One study that had a larger sample size and better design found no change in vocal behavior following brief participation in sensory activities. The review concluded that although sensory and motor impairments are commonly found in autism, the interventions developed to address them have not been well validated. In the case of SIT, it was noted, "there exist so few studies that conclusions cannot be drawn" (Dawson and Watling, 2000). Little is known regarding which ages or subgroups of individuals are most likely to benefit from therapies addressing sensory and motor difficulties, and further research is recommended.

Hayes (2004/update 2008) conducted a review of the peer-reviewed literature for the purpose of evaluating the efficacy of SIT for children with learning disabilities or developmental delays. The literature search identified 10 studies that met the criteria for detailed review. One was a prospective, nonrandomized, controlled study of SIT for children with developmental delays. Another was a prospective, matched-pair, controlled trial of SIT combined with neurodevelopmental therapy for developmental delays. The other eight studies were prospective, randomized trials that evaluated SIT versus no therapy and/or versus another therapy (e.g., perceptual motor treatment for children with learning disabilities, reading delays, cerebral palsy or Down syndrome). All the reviewed studies involved small test and control groups (n=9 to n=52) of children who met strict inclusion and exclusion criteria relating primarily to the diagnosis of SI dysfunction. Outcome measures used in the studies relied on standardized tests of academic, cognitive and physical function. Six of the trials reported blinding of assessment to treatment. Six studies involved no follow-up after the post-treatment assessment, and two had less than four months of follow-up. There were also two meta-analyses included in the review. The review concluded that data from individual studies and results of two meta-analyses "fail to provide evidence that SIT is an effective treatment or improves long-term outcome for children with learning disabilities, Down syndrome, developmental delays or putative SI disorders" (Hayes, 2004/update 2008). It was also noted that there is insufficient evidence to evaluate SIT for children with autism.

The NRC Committee on educational intervention for children with autism assessment concluded that there is insufficient evidence of the effectiveness of SIT for autism. It is noted in the report that there is a paucity of research concerning SIT for autism and that these interventions have not yet been supported by empirical studies (NRC, 2001). Review of the literature indicates insufficient evidence regarding the efficacy of SIT in children with autism.

Vision Therapy: Vision therapy is a proposed optometric treatment method for developing efficient visual skills and processing. A variety of visual therapies, oculomotor exercises, colored filters, Irlen lenses and ambient prism lenses have been used in children with autism for the proposed intent to improve visual processing or visual-spatial perception (NRC, 2001). Review of the literature indicates that studies have not provided clear support for the treatment of ASD.

Summary

The autism spectrum disorders (ASD) are a range of complex behavioral disorders that are also referred to as pervasive developmental disorders (PDD). The disorders include: autism or autistic disorder, Asperger's syndrome, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified (PDD-NOS). All of the disorders are characterized by varying degrees of impairment in communication skills, reciprocal social interactions, and restricted, repetitive and stereotyped patterns of behavior, speech and interests.

ASD is associated with many genetic conditions; however, genetic testing for the majority of patients will have a very low yield unless the family history, medical history, presence of mental retardation, or dysmorphic or other findings on examination are suggestive of a diagnosable condition. In the presence of mental retardation or dysmorphic features, it is appropriate to test for fragile X syndrome. If Rett's disorder is suspected, then testing for mutations on gene MECP2 is appropriate.

There are no medical interventions that have been proven to be effective in achieving a cure for autism; however, the condition may be managed through a combination of behavioral, pharmacological and educational interventions. Educational services (e.g., including special education, some forms of behavior modification and other services) are the central and integral aspect of the treatment for ASD. Psychosocial interventions include parent training that involves behavior modification techniques and referral to support groups. It has been noted in the literature that there is no single approach that is best for all individuals with ASD.

Therapies that have not yet been proven to be effective in the treatment of ASD include, but are not limited to: auditory integration therapy, chelation therapy, cognitive rehabilitation, craniosacral therapy, dietary and nutritional interventions (e.g., elimination diets, vitamins), facilitated communication, holding therapy, hyperbaric oxygen therapy, immune globulin therapy, intensive intervention programs for autism, music therapy, secretin infusion, sensory integration therapy, and vision therapy.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
83890 [†]	Molecular diagnostics; molecular isolation or extraction
83891 [†]	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892 [†]	Molecular diagnostics; enzymatic digestion
83894 [†]	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide)
83896 [†]	Molecular diagnostics; nucleic acid probe, each
83897 [†]	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern)
83898 [†]	Molecular diagnostics; amplification, target, each nucleic acid sequence
83904 [†]	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83909 [†]	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis)
83912 [†]	Molecular diagnostics; interpretation and report
88248 [†]	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)
	Multiple/Varied

HCPCS Codes	Description
	Multiple/Varied

ICD-9-CM Diagnosis Codes	Description
299.00-299.91	Pervasive developmental disorders

[†]**Note:** Covered when medically necessary when used to report FMR1 or MECP2 gene mutation testing for autism spectrum disorders.

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
82705 ^{††}	Fat or lipids, feces; qualitative
86001 ^{††}	Allergen specific IgG quantitative or semiquantitative, each allergen
86003 ^{††}	Allergen specific IgE; quantitative or semiquantitative, each allergen
86005 ^{††}	Allergen specific IgE; qualitative, multiallergen screen (dipstick, paddle, or disk)
90283 ^{††}	Immune globulin (IgIV), human, for intravenous use
92065 ^{††}	Orthoptic and/or pleoptic training, with continuing medical direction and evaluation

92585 ^{††}	Auditory evoked potentials for evoked response audiometry and/or testing of the central nervous system; comprehensive
95075 ^{††}	Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance such as metabisulfite)
95965 ^{††}	Magnetoencephalography (MEG), recording and analysis; for spontaneous brain magnetic activity (eg, epileptic cerebral cortex localization)
95966 ^{††}	Magnetoencephalography (MEG), recording and analysis; for evoked magnetic fields, single modality (eg, sensory, motor, language, or visual cortex localization)
95967 ^{††}	Magnetoencephalography (MEG), recording and analysis; for evoked magnetic fields, each additional modality (eg, sensory, motor, language, or visual cortex localization) (List separately in addition to code for primary procedure)
96116 ^{††}	Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities), per hour of the psychologist's or physician's time, both face-to-face time with the patient and time interpreting test results and preparing the report
96118 ^{††}	Neuropsychological testing (eg, Halstead-Reitan Neuropsychological Battery, Wechsler Memory Scales and Wisconsin Card Sorting Test), per hour of the psychologist's or physician's time, both face-to-face time administering tests to the patient and time interpreting these test results and preparing the report
96119 ^{††}	Neuropsychological testing (eg, Halstead-Reitan Neuropsychological Battery, Wechsler Memory Scales and Wisconsin Card Sorting Test), with qualified health care professional interpretation and report, administered by technician, per hour of technician time, face-to-face
96120 ^{††}	Neuropsychological testing (eg, Wisconsin Card Sorting Test), administered by a computer, with qualified health care professional interpretation and report
97532 ^{††}	Development of cognitive skills to improve attention, memory, problem solving (includes compensatory training), direct (one-on-one) patient contact by the provider, each 15 minutes
97533 ^{††}	Sensory integrative techniques to enhance sensory processing and promote adaptive responses to environmental demands, direct (one-on-one), patient contact by the provider, each 15 minutes
99183 ^{††}	Physician attendance and supervision of hyperbaric oxygen therapy, per session
	Multiple/Varied

HCPCS Codes	Description
A4575 ^{††}	Topical hyperbaric oxygen chamber, disposable
C1300 ^{††}	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval
E1902 ^{††}	Communication board, non-electronic augmentative or alternative communication device
G0176 ^{††}	Activity therapy, such as music, dance, art or play therapies not for recreation, related to the care and treatment of patient's disabling mental health problems, per session (45 minutes or more)
J1459 ^{††}	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g. liquid), 500 MG (Effective 1/1/09)
J1561 ^{††}	Injection, immune globulin, (Gamunex), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1566 ^{††}	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1567 ^{††}	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), 500 mg (Deleted 1/1/08)
J1568 ^{††}	Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569 ^{††}	Injection, immune globulin, (Gammagard liquid), intravenous, nonlyophilized, (e.g., liquid), 500 mg
J1572 ^{††}	Injection, immune globulin, (Flebogamma), intravenous, nonlyophilized (e.g.,

	liquid), 500 mg
Q4097 ^{††}	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg (Deleted 1/1/09)
P2031 ^{††}	Hair analysis (excluding arsenic)
	Multiple/Varied

††Note: Experimental/Investigational, Unproven/Not Covered when used to report these services for the assessment or treatment of autism spectrum disorders.

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