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REVIEW

Autism Spectrum Disorder in the Genomic Era: A Comprehensive Review of Etiology, Precision Diagnostics, Clinical Outcomes, and Emerging Gene-Editing Therapies

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Abstract: Autism spectrum disorder (ASD) is a heterogeneous, lifelong neurodevelopmental condition characterized by deficits in social communication and restricted, repetitive behaviors. Over recent decades, diagnostic expansion and methodological advances have led to increased prevalence estimates and a deeper appreciation of phenotypic, etiological, and outcome heterogeneity. This review synthesizes evidence from 2015–2024 across epidemiology, clinical diagnosis, neurobiology, genetics, environmental risk factors, mortality, and treatment. We summarize robust genetic contributions, including polygenic risk from common variants and high-impact rare or de novo mutations converging on synaptic function, chromatin regulation, and neurodevelopmental pathways. Prenatal and perinatal environmental exposures such as maternal immune activation, air pollution, and selected teratogens interact with genetic susceptibility through inflammatory, oxidative, and epigenetic mechanisms to influence ASD risk. Neuroimaging and multimodal studies reveal altered cortical developmental trajectories and atypical large-scale network connectivity associated with core symptoms and common comorbidities. Mortality studies demonstrate increased all-cause and cause-specific mortality, particularly related to epilepsy, medical comorbidities, and injury, with highest risk observed in individuals with intellectual disability. Current treatments remain primarily symptomatic, with early, intensive, and individualized behavioral interventions providing the greatest functional benefit, while pharmacotherapy targets associated behavioral challenges. Emerging genomic technologies, including CRISPR-based approaches, offer powerful experimental models and potential precision therapies for selected monogenic or high-impact copy number variant–associated ASD, although substantial safety, delivery, and ethical challenges remain. We conclude by highlighting priorities for integrative longitudinal studies, mechanistic links between molecular and circuit-level dysfunction, and responsible translational pathways toward precision therapeutics.

Keywords: autism spectrum disorder, genomics, neurodevelopment, CRISPR gene editing, precision diagnostics

Introduction

Autism spectrum disorder (ASD) is a long-term neurodevelopmental condition that affects an individual's ability to socially interact, communicate, and engage in reciprocal conversations, including both verbal and non-verbal communication. Individuals with ASD often exhibit repetitive or restricted patterns of behavior, interests, and activities.[1] Historically, the term autism was first used in 1911–1912 by the Swiss psychiatrist Eugen Bleuler to describe withdrawal and self-focused symptoms observed in schizophrenia.[2] It originates from the Greek word αὐτός (autos), meaning "self". The term "autistic" was later adopted within the field of child psychology to characterize specific developmental and behavioral features.[3] ASD is one of the most widespread neurodevelopmental disorders among children. Advances in diagnostic criteria, screening

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practices, and awareness have contributed to a marked increase in reported prevalence over recent decades. According to the most recent data from the US Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network, CDC affects approximately 1 in 31 children in the United States, and it is almost four times more common in males than females.[4] Recently, the term ASD has been adopted by Diagnostic and Statistical Manual of Mental Disorders[5]. Getting a correct diagnosis of ASD helps a individual understand past difficulties, recognize his or her strengths, and obtain the right kind of help. Early identification of ASD on the basis of signs and symptoms can insure better therapy and treatment options. Genetic testing, neuroimaging, electroencephalogram (EEG), and metabolic screening have been the four major areas for diagnostic medical testing of children having ASD.[6] Amongst these the neuroimaging studies have contributed a lot to make available important information into the pathological changes that occur in the brain of patients with ASD.[7] An EEG test measures and records the electrical activity of brain. Metabolic testing focuses on inborn weakness of metabolism.[8] The accurate cause of ASD is currently unknown. ASD is a complex state and may arise as a product of environmental, genetic predisposition or non-genetic factors. Mutations in the sequence of genetic code result in abnormal brain development leading to structural and functional brain abnormalities. A number of environmental exposures have been discovered such as exposure to certain viruses- measles, rubella, mumps, and chemicals- thalidomide and valproic acid that triggers ASD.[9–11] Maternal exposure to air pollutants—particularly heavy metals (eg, lead, mercury, cadmium) and particulate matter ($PM_{2·5}$ and PM_{10}) has been consistently associated with an increased risk of autism spectrum disorder (ASD) in offspring. Epidemiological studies show that higher prenatal exposure to fine particulates is linked to altered neurodevelopment, reduced cognitive functioning, and a higher likelihood of ASD diagnosis.[12,13] Mechanistically, these pollutants can cross the placental barrier, generating oxidative stress, mitochondrial dysfunction, and systemic inflammation in the developing fetus. Heavy metals disrupt neuronal proliferation, synapse formation, and neurotransmitter regulation. Moreover, particulate matter and toxic metal ions can activate maternal immune activation (MIA) pathways, increasing the production of pro-inflammatory cytokines such as IL-6 and TNF-α, which subsequently alter fetal brain development.[14,15] Additionally, prenatal exposure to air pollution has been shown to induce epigenetic modifications, including DNA methylation changes in genes involved in neurodevelopment and immune regulation, further contributing to ASD risk. Together, these findings highlight the biological plausibility and growing evidence linking maternal air pollutant exposure to ASD via oxidative stress, immune dysregulation, and epigenetic disruption.[16,17] Twin studies demonstrate strong genetic contributions to ASD, with concordance estimates approaching 80–90% in monozygotic twins compared with substantially lower rates in dizygotic twins, underscoring the central role of heritable factors.[18] Educational and developmental interventions, including applied behavior analysis (ABA) and the Early Start Denver Model (ESDM), form the cornerstone of ASD management. More recently, advances in molecular genetics have led to exploration of gene-editing technologies, including CRISPR-Cas–based approaches, as experimental tools to model ASD-associated mutations and, potentially, to correct specific pathogenic variants in selected monogenic forms of ASD.[19–21]

History

Initially the word autism was used in 1911 to illustrate the symptoms of the most severe cases of schizophrenia.[22] Indeed, some of the cases of Autism which were taken from symptoms of schizophrenia described withdrawn symptoms and social interaction problems were included in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) under the name Infantile Autism.[22] This was later changed to autism in the revised DSM-III.[22,23] In 1944, milder form of autism was described which is now known as Asperger's syndrome.[24] The very first case of autism was reported in 1938. It was Donald Triplett who was diagnosed with autism for the very first time.[25] Later on in 1950s, it was believed that autism is caused by cold and uncaring mothers who were labeled as "Refrigerator Mothers". However, in 1960s "Refrigerator Mothers" theory was disproved which states that it is caused by lack of maternal warmth. Furthermore, it was a general belief that lack of proper parenting had no role in occurrence of autism and it was caused due to neurological disturbance and other genetic ailments.[26] Then in 1980, initial behavioral therapies were used primarily in the treatment of children suffering from autism and later on autism was finally classified separately from schizophrenia.[27,28] In the same year, Thimerosal (a mercury-based preservative) was removed from all routinely given childhood vaccines as it was suspected to cause autism. However, the vaccine-autism link has been debunked.[29] Finally,

in 2013, DSM-V folds all subcategories of condition (Asperger's Syndrome and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) into one umbrella diagnosis of ASD.[30]

Genetics of Autism

Genetic factors constitute the largest contribution to ASD risk, with evidence indicating that most genetic liability arises from common inherited variants rather than rare de-novo mutations.[31,32] The most frequently appeared genes related to common variants include GRIN2B, AVPR1A, the oxytocin receptor gene (OXTR), the serotonin transporter–linked promoter region (5-HTTLPR), engrailed homeobox 2 (EN2), and GABR3.[33] The GRIN2B gene, which encodes the NR2B subunit of the NMDA glutamate receptor, plays a central role in synaptic development, neuronal plasticity, and cortical maturation. Loss-of-function GRIN2B mutations are strongly associated with global developmental delay, intellectual disability, and impaired cortical organization, whereas gain-of-function mutations enhance NMDA receptor activity and are linked to epilepsy and excitatory–inhibitory imbalance. Importantly, both loss- and gain-of-function GRIN2B variants have been repeatedly implicated in ASD, supporting the idea that disruptions in glutamatergic signaling contribute to core autistic phenotypes.[34] The AVPR1A gene mediates the central effects of arginine vasopressin, a neuropeptide involved in social cognition and affiliative behavior. Polymorphisms in AVPR1A have been consistently linked to social interaction deficits, a defining feature of ASD.[35,36] Similarly, variation in the serotonin transporter gene, particularly the short (S) allele of the serotonin transporter–linked promoter region, has been associated with social impairment and altered emotional regulation in ASD.[37,38] GABR3 is confined to chromosome 15q11-q13 which is said to be related with gene expression and also recombination. Deletion of this site canleadsto monogenic causes of ASD.[39] In addition to common variants, approximately 3% of ASD cases are attributed to rare inherited mutations. Genes frequently implicated in this category include SHANK3, neurexin 1 (NRXN1), forkhead box P2 (FOXP2), CDH8, and SYNGAP1.[40–42] SHANK3 is a main autism candidate gene where mutations occur between 1–2% of individuals with ASD. SHANK3 codes for a protein essential for normal functioning of the synapse.[43] NRXN1 interacts with neuroligin-3 and SHANK3 to create risk for autism and mental retardation. FOXP2 has appeared as one of the key candidate linking autism and language.[44] FOXP2 was determined in individuals who had an inherited speech disorder.[45] An additional ~3% of ASD risk arises from de novo mutations, which are not inherited from either parent. These include single-nucleotide variants and copy number variations (CNVs) involving deletions or duplications of large genomic regions. Pedigree and sequencing studies have identified at least 12 recurrent CNVs that segregate with ASD in affected families, underscoring the contribution of rare but highly penetrant genetic events to ASD susceptibility.[46–48]

Spread

Early epidemiological studies of "autism" in the 1960s and 1970s (eg Victor Lotter 1966) reported very low prevalence roughly 2–4 cases per 10,000 children (0.02–0.04%) in Europe and the United States.[49] Over time, as diagnostic criteria expanded and the concept of ASD was adopted, estimates rose sharply. For example, in a large population-based study from South Korea on school-age children (7–12 years), the prevalence of ASD was estimated at 2.64% (approximately 1 in 38 children).[50,51] By 2022, data from Centers for CDC's ADDM Network in the United States indicated an ASD prevalence of 32.2 per 1000 children (≈ 1 in 31 children, or ~3.2%) among 8-year-olds.[52] Globally, a recent study estimated that in 2021 approximately 1 in 127 individuals worldwide, across all ages, were on the autism spectrum.[53] A 2022 meta-analysis reported an overall global prevalence among children of approximately 0.6–1.0%, with considerable variation across regions.[54] Therefore, the available evidence demonstrates a dramatic rise in reported autism/ASD prevalence from a rare disorder in early reports (0.02–0.04%) to current estimates suggesting roughly 0.6–3% in children, depending on population and diagnostic practice. In Portugal, the frequency of the disorder was found to be 9.2 per 10,000 children.[55] During the year 2010 the overall probable autism incidences were 14.7 per 1000 (1 in 68) children age 8 years. The prevalence of autism in some other countries like Denmark is 4.3%, Indonesia-14.8%, Norway-5.2%, Australia-35.7%, Israel-10.0%, Swedish-11.5%, USA- 3.4%, and Ireland- 4.3%[56] (Figure 1). These disparities underscore the influence of diagnostic criteria, surveillance systems, and sociocultural factors on ASD prevalence estimates.

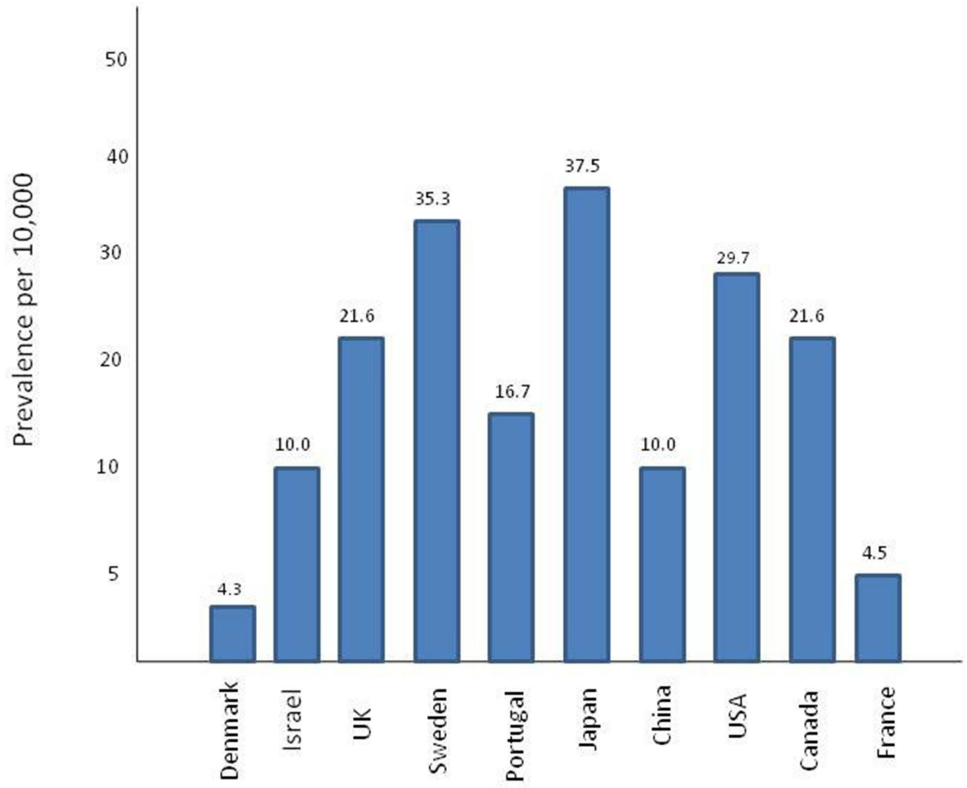

Figure 1 Prevalence of autism spectrum disorder (ASD) among children in selected countries as reported in population-based epidemiological studies from the 1960s to 2022.
Notes: Prevalence estimates are shown as reported in the original studies (per 1000 children, percentages, or ratios) and reflect differences in diagnostic criteria, study design, age groups, and geographic regions.

Gender Specific Data

ASD are recently less diagnosed in females than males, with ratio of 1:4.[57] As stated by female protective effect hypothesis, females need more severe genetic mutations to develop autism as compared to male.[58,59] Some studies have shown that there is a social discrimination that elevates the possibilityof diagnosis in males, while another research revealed that there are sex-based distinction in genetic susceptibility.[60,61] Large-scale sequencing studies later confirmed that females with ASD carry a significantly greater load of deleterious copy-number variants (CNVs) than males.[62] Similarly, rare deleterious single-nucleotide variants (SNVs) were found to be more frequent and severe in autistic females compared to autistic males, indicating a higher genetic threshold required for clinical presentation.[63,64] Together, these findings reinforce the idea that the female brain requires more substantial genetic disruption to develop ASD, whereas males exhibit ASD traits with a comparatively lower mutational burden. This genetic asymmetry, combined with potential social, diagnostic, and behavioral masking differences, contributes to the persistent underdiagnosis of ASD in females.[64,65]

Symptoms of Autism Spectrum Disorder

The ASD is defined by persistent deficits in social communication and social interaction, accompanied by restricted, repetitive patterns of behavior, interests, or activities (RRBs), as outlined in the DSM-5-TR (2022).[66] These symptoms must be present from early development and lead to clinically significant impairment in functioning. Individuals with ASD consistently demonstrate impairments in the intuitive processing of social cues. These include reduced or atypical use of eye contact, facial expressions, gestures, and other non-verbal communicative behaviors essential for reciprocal social engagement. Difficulties forming and sustaining age-appropriate peer relationships and diminished sharing of emotions or interests are also characteristic. Wing and Gould's early framework of social interaction subtypes remains

foundational,[67] and recent neuroimaging studies show atypical activation in social-cognitive networks such as the superior temporal sulcus and medial prefrontal cortex.[68] Communication impairments in ASD extend beyond delayed language acquisition to include abnormalities in pragmatic language, conversational reciprocity, and comprehension of figurative or implied meaning. Early descriptions by Tager-Flusberg (1996) remain widely cited, noting echolalia, unusual prosody, and limited symbolic play.[69] Contemporary evidence indicates that pragmatic language deficits remain among the most persistent symptoms into adolescence and adulthood.[70] These impairments are linked to disruptions in networks supporting language integration and executive function. RRBs represent a broad phenotype that includes motor stereotypies (eg, hand-flapping, rocking), insistence on sameness, circumscribed interests, and repetitive use of objects such as lining up, spinning, or sorting items. Updated DSM-5-TR criteria explicitly include sensory processing abnormalities, such as hypersensitivity or hyposensitivity to sound, light, touch, and pain. Recent sensory research shows that 60–90% of autistic individuals experience atypical sensory reactivity, which is strongly associated with anxiety and behavioral rigidity.[70] Although not part of the core diagnostic criteria, individuals with ASD frequently exhibit hyperactivity, impulsivity, aggression, irritability, self-injurious behaviors, and sleep and feeding disturbances. These associated symptoms can significantly worsen functional outcomes. For instance, meta-analytic evidence indicates that sleep disorders affect 40–80% of children with ASD, contributing to worsening daytime behavior and cognitive performance.[71] Aberrant sensory-motor regulation and emotional dysregulation also contribute to these difficulties. Overall, contemporary research conceptualizes ASD symptoms as arising from disruptions in social motivation, predictive coding, and sensory processing, combined with atypical connectivity in large-scale brain networks. Multimodal neuroimaging studies (2019–2024) highlight consistent patterns of altered functional connectivity in the default mode network, salience network, and sensory integration circuits.[72,73] These mechanistic insights strengthen the understanding of how social, communicative, and repetitive-behavior symptoms emerge across development.

Causes of ASD

ASD is a multifactorial neurodevelopmental condition with no single identified cause; current evidence supports a model in which genetic, environmental, and neurobiological factors interact to produce the characteristic behavioral phenotype. Early syntheses emphasized this complexity and proposed interacting genetic and environmental pathways affecting neurite outgrowth, synaptogenesis and neuronal migration[74] (Figure 2).

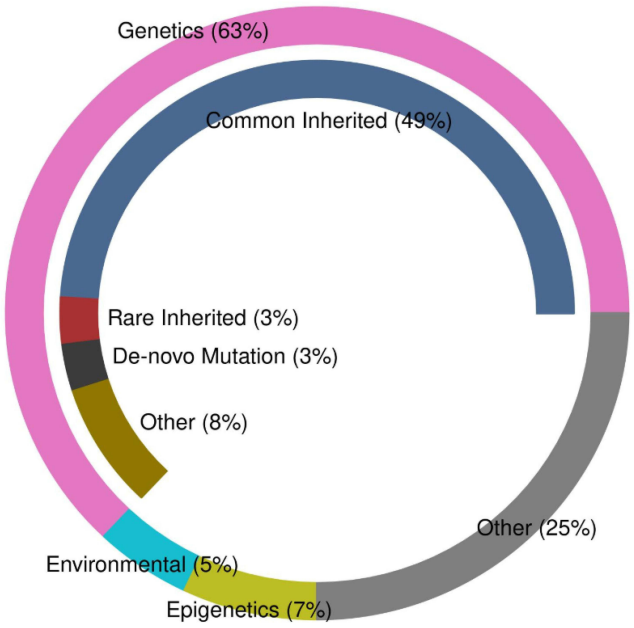

Figure 2 Schematic representation of the multifactorial etiology of autism spectrum disorder (ASD), illustrating the interaction between genetic susceptibility, environmental exposures, and epigenetic and neurobiological mechanisms contributing to altered neurodevelopment.

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Genetic Factors

Genetics contribute strongly to ASD risk but the architecture is complex and heterogeneous: both common inherited variants (polygenic risk) and rare de novo or inherited variants (copy-number variants, disruptive single-nucleotide variants) are implicated. Large genetic studies indicate that common variation explains a substantial fraction of population liability while rare, often highly penetrant mutations explain many individual cases. Recent reviews summarize the broad genetic heterogeneity and gene-network convergence on synaptic, chromatin-remodeling, and transcriptional pathways.[75,76]

Familial Aggregation and Recurrence

Family and twin studies demonstrate high heritability and familial clustering. Population-based analyses report high concordance in monozygotic twins and substantially lower concordance in dizygotic twins, consistent with strong genetic contribution modified by nonshared environment. A large Swedish cohort estimated cumulative ASD probability of ~59% in monozygotic twins vs ~13% in dizygotic twins; sibling recurrence and broader familial relative risks are elevated but variable across studies. Contemporary cohort and sibling studies (including meta-analyses) provide detailed recurrence-risk estimates and show increased risk for later siblings, especially male siblings.[77,78]

Neurobiological Mechanisms

Neurodevelopmental studies link genetic and prenatal insults to altered brain growth trajectories and circuit formation. Histological, imaging, and molecular work indicate early differences in neuronal proliferation, migration and synaptogenesis; altered cortical and subcortical structure and atypical white-matter maturation are commonly reported. Structural MRI studies in children with ASD show regional increases in gray matter (particularly frontal/temporal regions) and differences in gray–white matter boundary and maturation trajectories; these changes likely reflect disrupted early cortical development and connectivity.[78,79]

Prenatal and Perinatal Environmental Risks

Epidemiological evidence implicates several prenatal/perinatal exposures that modestly increase ASD risk and likely interact with genetic susceptibility. Well-supported risk factors include advanced parental age, maternal infection/fever during pregnancy, preterm birth/very low birth weight, and obstetric complications (eg, perinatal hypoxia). Recent systematic reviews and meta-analyses quantify these associations: maternal infection/fever during pregnancy is associated with ~1.3-fold increased ASD risk in pooled analyses, while advanced parental age shows a reproducible, dose-dependent association across studies.[80,81]

Air Pollution, Pesticides and Chemical Exposures

A growing body of epidemiologic work links prenatal exposure to ambient air pollution (notably $PM_{2.5}$ and traffic-related pollutants) and certain pesticides/insecticides to increased ASD risk, although effect sizes vary and some cohort studies report null findings. Large cohort syntheses (including the ESCAPE cohorts and recent meta-analyses) report modestly elevated odds (eg, pooled ORs ~1.3–1.4 for several pollutants), and animal/mechanistic studies indicate plausible biological pathways (placental transfer, oxidative stress, immune activation, epigenetic changes).[82] Maternal organochlorine and organophosphate insecticide exposure and certain neonicotinoids have also been associated with neurodevelopmental outcomes in offspring in case-control and prospective studies, but causality remains to be fully established.[83]

Gene–Environment Interplay and Epigenetics

Current models emphasize that genetic vulnerability modifies susceptibility to environmental exposures, and vice-versa. Environmental insults (infections, pollutants, maternal immune activation) can provoke oxidative stress, inflammation, mitochondrial dysfunction, and epigenetic alterations (eg, DNA methylation changes) that perturb gene expression during critical windows of brain development. Integrative studies combining genomics with exposure data increasingly support interaction effects, though large, well-powered prospective cohorts are still needed to map specific gene × environment relationships.[84]

Mortality

Individuals with ASD experience substantially elevated premature mortality compared with the general population: meta-analyses and large cohort studies report overall standardized mortality ratios (SMRs) and relative risks generally showing more than double the all-cause mortality (SMRs ≈2–3), with even higher ratios for autistic people who have co-occurring intellectual disability (SMRs often >3–5).[85] Life-expectancy analyses and life-years-lost estimates confirm this pattern: autistic people without intellectual disability show a measurable reduction in life expectancy (several years on average), while those with intellectual disability incur substantially larger losses.[86] Epilepsy is a leading contributor to premature death prevalence of epilepsy in ASD is estimated at roughly 20–30%, and seizure-related mortality (including sudden unexpected death in epilepsy) disproportionately affects younger autistic individuals and those with intellectual disability.[87]

External causes and injuries also account for a large share of excess mortality: children and adolescents with ASD have markedly increased risk of fatal unintentional injury (notably drowning), and suicide and self-harm have been shown to contribute to excess deaths in older adolescents and adults.[88] Recent systematic reviews (2022–2024) that synthesize cause-specific patterns report consistent excess mortality across natural (neurological, respiratory, circulatory, infectious) and unnatural causes, though absolute rates and cause distributions vary by study design, age composition, presence of intellectual disability, and geographic setting.[89] Importantly, newer analyses using life-table methods and large administrative cohorts (UK, Sweden, Denmark, US) have refined estimates of years of life lost and shown that comorbidities, seizure burden, diagnostic subgroup, and gaps in preventive care and safety (eg, wandering supervision, water safety) are key modifiable contributors to mortality disparities—underscoring the need for seizure management, injury-prevention programs (water safety, elopement prevention), mental-health supports, and improved healthcare access to reduce excess mortality in ASD populations.[86]

Diagnosis

Clinically, ASD is diagnosed on the basis of core symptoms. Most autisms are diagnosed in early childhood. Percentage distribution of child's age is 6–17 years, getting autism diagnosis is shown in (Figure 3). ASD is diagnosed

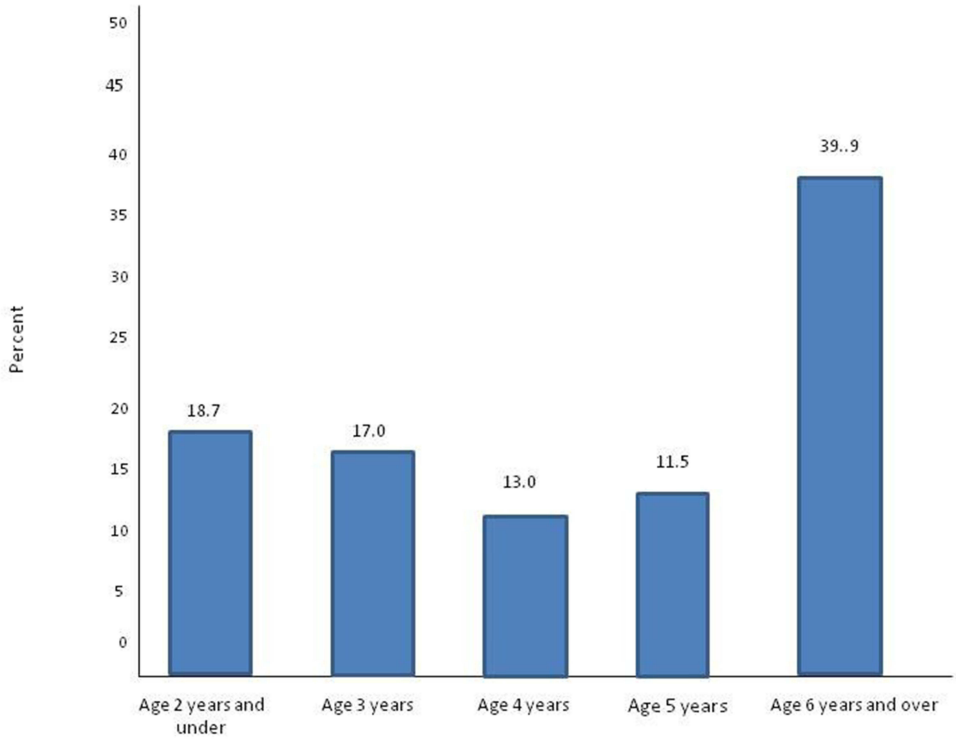

Figure 3 The bar graph depicts the percentage of children aged 6–17 years getting diagnosed with autism. Maximum (40%) children were around 6years and above. On the otherhand, minimum (13%) children were around 4 years.

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clinically based on persistent deficits in social communication and restricted, repetitive behaviors, as defined by the DSM-5-TR (2022). Most diagnoses occur in early childhood, although increasing awareness and improved screening tools have contributed to rising detection rates in adolescents and adults. Early developmental screening between 18–24 months is recommended by major pediatric guidelines, with diagnostic confirmation based on structured behavioral assessments such as the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and the Autism Diagnostic Interview–Revised (ADI-R), which remain the gold standards in current clinical practice.[90] Modern clinical evaluation includes genetic testing, neuroimaging when indicated, and select metabolic screening. Chromosomal microarray analysis (CMA) is currently recommended as the first-tier genetic test for children diagnosed with ASD, as it detects submicroscopic deletions or duplications—known as copy-number variants (CNVs)—with a diagnostic yield of approximately 10–20%, superior to older methods such as karyotyping or fragile X testing.[91] More recently, whole-exome sequencing (WES) has been adopted as a complementary or second-tier test because it identifies single-nucleotide variants in ASD-associated genes and increases the diagnostic yield to 30–40% in some cohorts.[92] Neuroimaging is not used to diagnose ASD but is performed when neurological abnormalities, seizures, or regression prompt evaluation for structural brain disorders. Structural MRI identifies abnormalities in a minority of cases and is recommended selectively (American Academy of Neurology/AAP guidelines). Functional imaging (fMRI, PET, MEG) has advanced understanding of ASD neurobiology—including alterations in social-cognitive networks—but remains a research tool, not a diagnostic test.[93] Metabolic screening is performed only when history or examination suggests an underlying inborn error of metabolism. Recent guidelines emphasize targeted testing rather than universal screening, as metabolic disorders account for <1% of ASD cases.[94] Contemporary ASD diagnosis relies primarily on behavioral assessment, supported by genomic testing for etiological clarification, and selective use of neuroimaging or metabolic testing. Advances in genetic sequencing and updated clinical guidelines continue to improve diagnostic precision and early identification.

Treatment and Therapies

ASD lacks a curative therapy; however, convergent evidence from randomized trials, longitudinal cohort studies, and meta-analytic data supports early, intensive, multimodal intervention as the most effective strategy for modifying developmental trajectories. Contemporary clinical management combines evidence-based behavioral and developmental interventions, speech-language therapy, occupational and physical therapy, and targeted psychopharmacological treatment, delivered within an individualized, functionally oriented framework.[95] Utilization patterns of major therapeutic modalities among children aged 6–18 years are depicted in Figures 4 and 5. Applied Behavior Analysis (ABA) represents the most empirically substantiated modality, with strong effects on communication, social-adaptive functioning, and early cognitive outcomes through structured reinforcement-based learning algorithms.[19] Advanced ABA-derived models include Pivotal Response Treatment (PRT), which targets pivotal neural-behavioral domains such as motivation, self-regulation, and responsivity to multiple cues, thereby producing generalized behavioral gains[96] and Discrete Trial Training (DTT), a massed-practice, error-controlled instructional format that decomposes complex skills into discriminable behavioral units, improving accuracy and acquisition efficiency.[97] The ESDM integrates ABA principles with developmental neuroscience, targeting socio-communicative reciprocity, joint attention, and early language circuits in children aged 12–48 months; randomized controlled trials demonstrate significant improvements in IQ, adaptive behavior, and cortical activation profiles.[98] Speech-language therapy addresses impairments across expressive, receptive, and pragmatic domains, targeting phonological planning, morphosyntactic organization, prosody, symbolic communication, and social-pragmatic coherence.[99] Occupational therapy (OT) and sensory integration-based approaches address deficits in fine-motor coordination, visuomotor planning, executive sequencing, and sensory-motor modulation, thereby enhancing competence in activities of daily living such as writing, utensil use, dressing, and school-related tasks.[100] Physical therapy (PT) focuses on gait, postural stability, motor coordination, balance, and proprioceptive control, compensating for motor-planning impairments prevalent in ASD.[101] As ASD has no disease-modifying pharmacotherapy, medication use is symptom-targeted; risperidone, the first FDA-approved agent for ASD-associated irritability, demonstrates efficacy in reducing severe aggression, self-injury, and behavioral dysregulation through dopaminergic and serotonergic blockade.[102] Collectively, current evidence supports a neurodevelopmentally informed, interdisciplinary

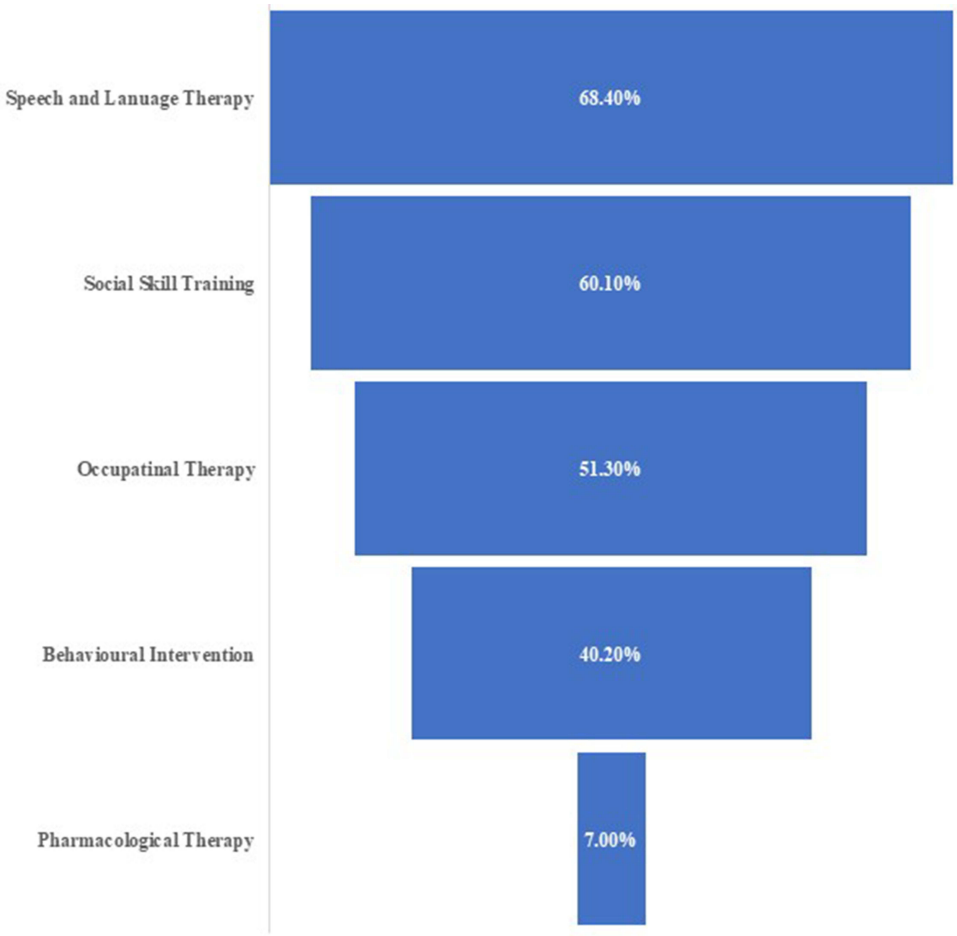

Figure 4 Distribution of therapeutic interventions used among children aged 6–11 years with autism spectrum disorder (ASD), categorized by type of treatment.

treatment paradigm integrating behavioral, therapeutic, and psychopharmacological modalities to optimize functional outcomes and mitigate ASD-related morbidity across developmental stages.

CRISPR Mediated Gene Editing for Treatment of Autism

CRISPR-based genomic perturbation has become a powerful tool to dissect ASD genes and to test causal links between genotype and phenotype in cellular and animal models. Seminal work used CRISPR/Cas9 to generate heterozygous CHD8 loss-of-function human iPSC lines and showed that CHD8 regulates transcriptional networks enriched for ASD risk genes and neurodevelopmental pathways, providing mechanistic evidence that CHD8 haploinsufficiency contributes to ASD-relevant neurodevelopmental changes.[20] CRISPR strategies have also been used to model and functionally interrogate 16p11.2 locus genes (KCTD13) and to perform multiplexed disruption of autism-susceptibility genes in neurons or organoids, yielding insight into convergent molecular pathways (synaptic, chromatin, and MAPK/CUL3-related pathways).[103,104] Importantly, proof-of-principle therapeutic editing in the central nervous system has been demonstrated in rodents: intracranial nanoparticle delivery of Cas9 RNPs (CRISPR-Gold) reduced striatal mGluR5 expression and ameliorated exaggerated repetitive behavior in fragile X mouse models, demonstrating that non-viral, localized editing can reverse disease-relevant behaviors in adults.[105] Recent technological advances accelerate movement from gene-perturbation studies toward potential somatic therapies while also clarifying major hurdles. Base editors and prime editors permit precise single-base changes or small insertions/deletions without double-strand breaks, and 2023–2024 studies show increasingly efficient prime/base editing in vivo in brain tissue (AAV and LNP delivery platforms achieving clinically relevant editing levels in mouse brain), pointing to viable routes for correcting specific

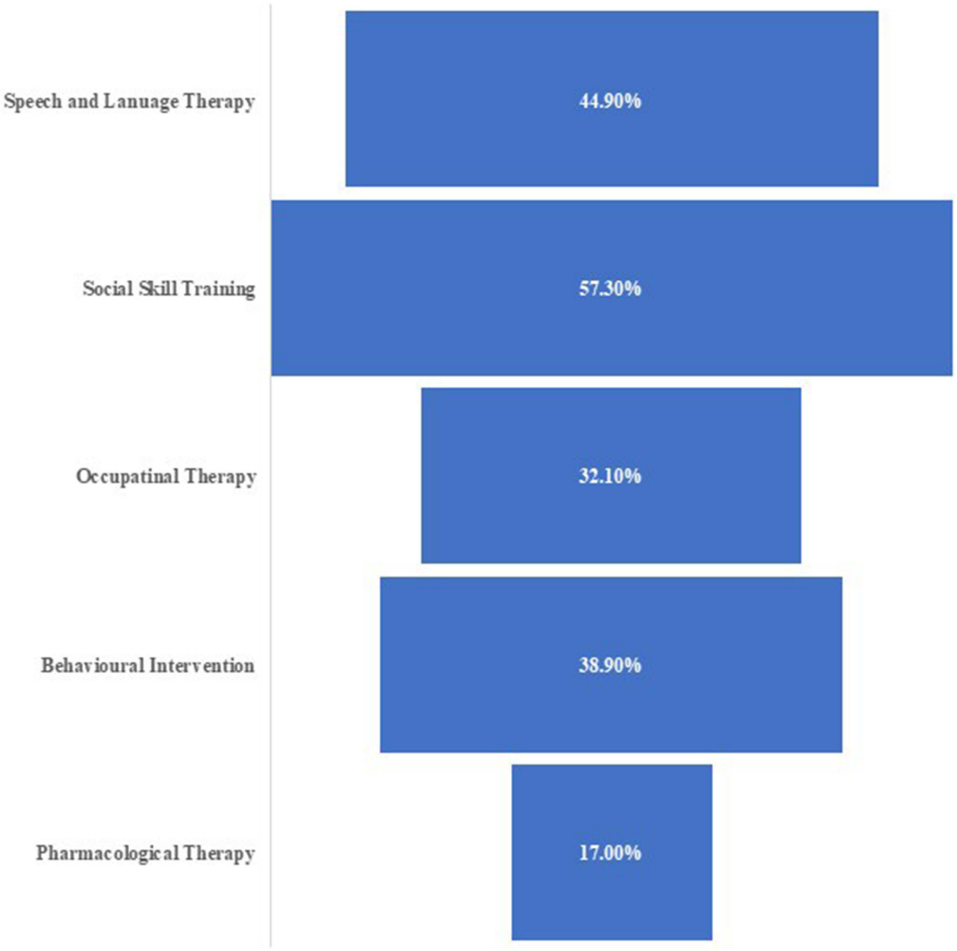

Figure 5 Distribution of therapeutic interventions used among children aged 12–17 years with autism spectrum disorder (ASD), categorized by type of treatment.

pathogenic single-nucleotide variants that underlie some syndromic forms of ASD.[106,107] Reviews synthesize that CRISPR activation/repression (CRISPRa/i), antisense oligonucleotides (ASOs), and gene-replacement strategies expand the therapeutic toolbox beyond nuclease editing for disorders of haploinsufficiency or dominant negatives.[108] However, key translational challenges remain: (1) efficient, safe, and brain-wide delivery across the blood–brain barrier without neurotoxicity; (2) control of off-target edits, immune responses, and mosaicism; (3) determining which ASD etiologies (monogenic syndromes such as fragile X, Rett, or specific 16p11.2 CNV cases) are realistically targetable versus complex polygenic ASD; and (4) ethical and regulatory constraints around germline editing and irreversible CNS modification. Current consensus in reviews is that CRISPR therapeutics for ASD are promising but still preclinical: several in vivo successes exist, yet no CRISPR-based therapy for autism has entered human trials as of 2024, and clinical translation will require durable safety data, precision delivery platforms, and careful patient selection.[108,109]

Conclusion

ASD exemplifies a complex neurodevelopmental condition in which diverse genetic architectures and environmental influences interact across developmental windows to produce heterogeneous clinical trajectories. Progress in genomics, neuroimaging, and systems neuroscience has illuminated convergent molecular and circuit-level substrates, supporting a shift toward biologically informed, individualized care. The greatest clinical impact is likely to arise from improved early identification and stratification, particularly through the development and validation of non-invasive biomarkers such as advanced neuroimaging, electrophysiological, and genomic profiling approaches. These tools offer realistic opportunities to refine diagnosis, predict developmental outcomes, and guide personalized intervention during critical

periods of brain development. In parallel, emerging gene- and circuit-directed therapies, including CRISPR-based gene-editing technologies, represent promising but longer-term strategies that are currently best suited for well-defined monogenic or high-impact copy number variant–associated forms of ASD. While preclinical studies demonstrate proof-of-concept efficacy, substantial challenges related to safety, delivery, off-target effects, and ethical considerations must be addressed before clinical translation. Future research priorities should integrate longitudinal, population-representative cohorts linking early biomarkers to clinical outcomes, alongside rigorous preclinical and translational pipelines for precision molecular therapies. Balancing near-term advances in early diagnosis with responsible development of gene-based interventions will be essential to achieving meaningful and equitable improvements in outcomes for individuals with ASD.

Data Sharing Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published.

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Disclosure

The authors declare that they have no conflicts of interest related to this work.

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