

Autism Etiology and Individualized Care

A review of evidence and the limits of percentage based treatment selection

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ABSTRACT

Families encounter competing explanations of autism and treatments promoted as correcting an underlying cause. A percentage breakdown could appear useful, but genetic liability, metabolic findings, environmental exposures, and treatment response describe different quantities and can overlap within the same child. My objective in this study is to examine which quantitative statements about autism etiology are defensible and how this evidence should inform expectations for individualized care. I use a targeted narrative review examining human genetic, epidemiological, mechanistic, and intervention research, together with clinical guidance and regulatory updates available in May 2026. Including reported estimates were retained with their original denominators and study contexts; incompatible measures were not pooled. My findings were that a large multinational study estimated autism heritability at 80.8%. Clinical genetic testing identifies explanatory findings in a smaller, selected proportion. No validated population fraction can be assigned to impaired methylation, blood–brain barrier dysfunction, or generalized chemical exposure. Small methylcobalamin and folinic-acid trials do not establish causal subtypes. However FOLR1-related cerebral folate transport deficiency provides a specific example of a treatable genetic disorder. Large studies and current international review evidence do not seem to support vaccines as a cause of autism. A direct study on the topic needs to be done for more details. Etiologic information can sometimes change care, but treatment should be selected by clinical findings, credible evidence, and meaningful goals. Nonresponse to a supplement does not diagnose another cause or establish that further experimental therapies will help.

Keywords: *autism spectrum disorder; genetics; heritability; methylation; cerebral folate deficiency; blood–brain barrier; environmental exposures; treatment response*

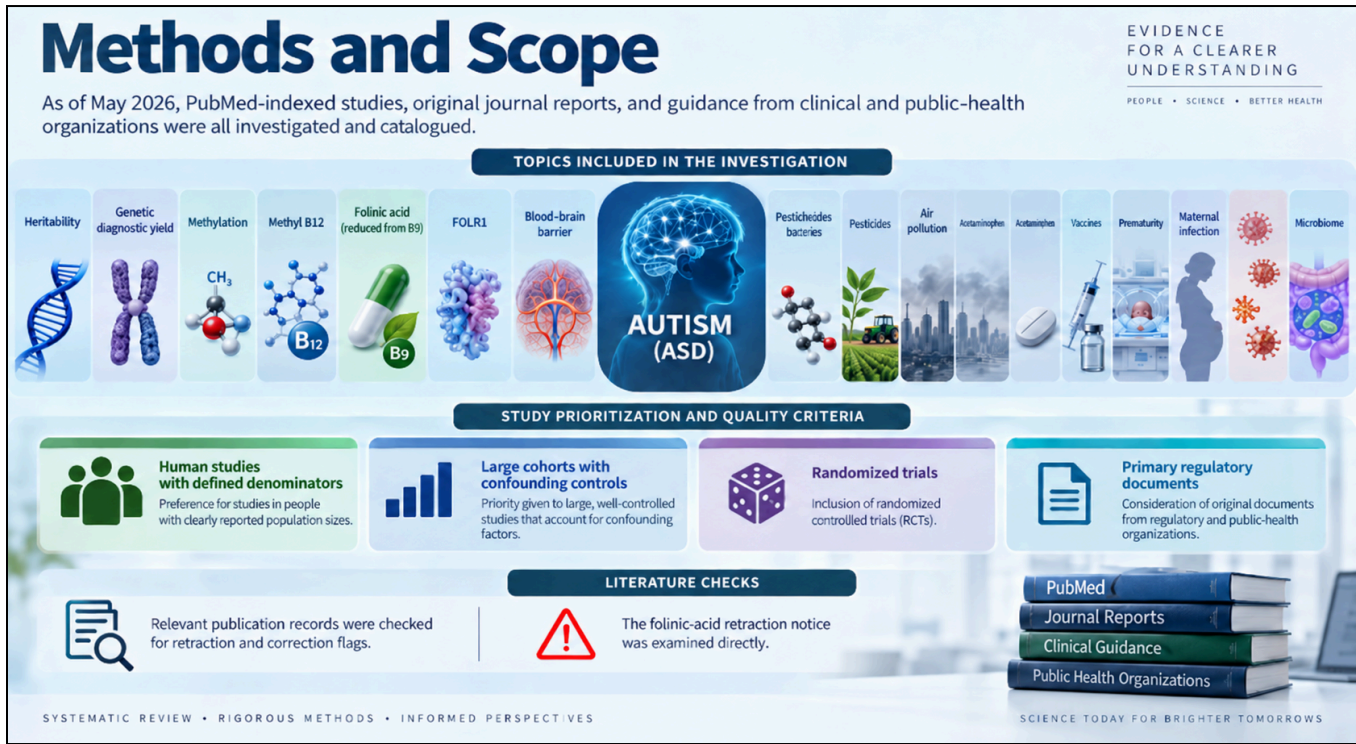
Introduction

Autism spectrum disorder (ASD) is identified through developmental history and behavior, with substantial variation in communication, sensory experiences, adaptive skills, and support needs. The phrase “children born with autism” is not a routinely measured diagnostic category: developmental influences may begin prenatally, but autism is generally recognized later. Consequently, the relevant evidence concerns children subsequently diagnosed with ASD, rather than a neonatal test establishing its cause. [1]

The central clinical question is understandable: if one child benefits from a biological treatment and another does not, could different underlying mechanisms explain the difference? Sometimes they could. However, that possibility does not justify assigning children to unvalidated categories or interpreting a failed treatment as evidence for a different category. This review examines genetics, methylation and folate metabolism, brain barriers, environmental exposures, vaccines, and additional developmental associations. Its purpose is to make the uncertainty usable for families without converting hypotheses into diagnoses.

Methods and scope

I made sure to obtain data as up to date as May 2026 from PubMed-indexed studies, original journal reports, and guidance from clinical and public-health organizations that were all investigated, documented, catalogued and compared. This investigation combinations included autism with heritability, genetic diagnostic yield, methylation, methyl B12, folinic acid (reduced from B9), FOLR1, blood–brain barrier, valproate, pesticides, air pollution, acetaminophen, vaccines, prematurity, maternal infection, and microbiome. Priority was given to human studies with defined denominators, large cohorts with confounding controls, randomized trials, and primary regulatory documents. Relevant publication records were checked for retraction and correction flags; the folinic-acid retraction notice was examined directly.



What percentages can and cannot measure

A heritability estimate describes how much population variation in an underlying liability is statistically associated with genetic differences under a particular model. It is not a fraction of an individual child’s autism, the percentage of affected children with a single genetic diagnosis, or a prediction that treatment cannot help. Its complement is not a measured percentage of autism caused by chemicals, vaccines, or nutritional problems. [2]

Genetic diagnostic yield instead counts tested children who receive an explanatory molecular finding. Exposure-specific absolute risk counts diagnoses among exposed children over a stated period. Treatment response counts or measures improvement among trial participants under a specific intervention. These denominators cannot be interchanged. A population-attributable fraction asks a further, counterfactual question: how many cases might not occur if an exposure were removed? Estimating it requires a defensible causal effect and exposure distribution, rather than a biomarker frequency or a relative-risk estimate alone.

The proposed categories also occur at different biological levels. A genetic variant can affect folate transport or gene regulation, while illness or dietary restriction can alter blood biomarkers. Thus, “genetic,” “methylation-related,” and “barrier-related” need not describe separate children. Table 1 deliberately has no total row.

Table 1. Quantitative evidence relevant to proposed autism causes and mechanisms

Domain	Defensible quantitative statement	Meaning and limitation
Genetic contribution	Heritability 80.8% (95% CI 73.2–85.5%) in a five-country study. [2]	Population liability estimate; About 80% of the differences in autism risk across the population were statistically associated with inherited genetic differences
Identifiable genetic findings	CMA: 24/258 (9.3%); WES: 8/95 (8.4%); combined testing: 15/95 (15.8%). [3]	Historical clinical cohort. Yield varies with selection and testing; these percentages cannot be added.
Methylation or one-carbon metabolism	Percentage of ASD caused by dysfunction: not established. [4,5]	Group biomarker differences do not define a causal subgroup or predict supplement benefit.
Cerebral folate transport deficiency	Fraction of all ASD attributable to FOLR1-related disease: not established. [6,7]	A specific rare genetic disorder; distinct from nonspecific “methylation problems.”
Blood–brain barrier dysfunction	Population causal percentage: not established. [8]	Small postmortem studies provide mechanistic clues, not population prevalence or a clinical screening test.
Prenatal valproate exposure	Estimated ASD risk by 14 years: 4.42% among 508 exposed children; 1.53% in the entire cohort. [9]	Risk among exposed children, not the percentage of all ASD caused by valproate; overall cohort is not an unexposed comparator.
Pesticides and air pollution	No single established percentage attributable to “chemicals.” [10,11]	Associations depend on agent, dose proxy, timing, and study design; causality and individual attribution remain uncertain.
Prenatal acetaminophen	Sibling-controlled ASD HR: 0.98 (95% CI 0.93–1.04) in Sweden; 1.00 (0.91–1.11) in Hong Kong. [12,13]	Neither analysis detected increased risk; hazard ratios are not percentages of cases caused.
Childhood vaccines	No demonstrated causal contribution. MMR HR: 0.93 (95% CI 0.85–1.02). [14,15]	Strong evidence against a causal association; no evidence-based vaccine-caused ASD category.
Prematurity	ASD prevalence 6.1% at 22–27 weeks versus 1.4% at 39–41 weeks in a Swedish cohort. [16]	Prevalence within gestational-age groups, not an attributable fraction or proof of one individual cause.
Immune and microbiome findings	No validated universal causal percentage. [17,18]	Some associations weaken with confounding control; observed changes can follow other characteristics.

CMA, chromosomal microarray; WES, whole-exome sequencing; HR, hazard ratio; CI, confidence interval. “Not established” is not a numerical zero and does not establish that a mechanism is causal. Vaccine evidence is stronger than simple absence of a prevalence estimate.

Genetics and the value of diagnostic evaluation

Bai and colleagues analyzed 2,001,631 individuals, including 22,156 with ASD. Their results support a substantial inherited contribution while leaving questions about gene–environment interplay unresolved. They do not imply that every family can obtain a molecular explanation. [2] Large sequencing studies also implicate multiple genes involved in developmental and neuronal processes, illustrating why genetics cannot be reduced to a single “autism gene.” Genetic changes can be inherited or arise de novo, so a genetic finding does not necessarily imply that a parent carries the same variant. [19]

In the Tammimies cohort, the combined CMA and WES yield was 15.8% among the 95 children receiving both tests (95% CI 9.1–24.7%); two children had findings on both tests. This directly demonstrates overlap between diagnostic methods. The figure is a study-specific historical yield, not a current ceiling on the genetic contribution to ASD. A negative result leaves many possible genetic contributions unresolved. [3]

The AAP recommends offering an etiologic genetic evaluation. The ACMG recommends considering exome or genome sequencing as a first- or second-tier test for children with congenital anomalies, developmental delay, or intellectual disability; that recommendation is not interchangeable with a universal sequencing algorithm for isolated ASD. Test choice should reflect the child’s phenotype and available expertise. [20,21] Identifying a disorder can guide surveillance and counseling even when it does not produce an autism-specific drug treatment.

Methylation findings and supplement response

Methylation is a family of chemical reactions, not an on–off process that can be labeled simply “broken.” Folate and vitamin B12 participate in one-carbon metabolism, while DNA methylation is a gene-regulatory modification. Blood metabolites used to estimate methylation capacity and methylation marks measured at individual DNA sites therefore represent related but different observations. [4,5]

James and colleagues compared 20 autistic children with 33 controls and reported differences in methionine-related and glutathione biomarkers, including a lower ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH). A small nutritional intervention normalized measured metabolic abnormalities. These observations generated a plausible hypothesis, but did not establish how many children’s autism was caused by that pathway or demonstrate that biochemical normalization reversed autism. [4] Wong and colleagues found ASD-associated methylation differences in a study of 50 identical-twin pairs. Such associations cannot by themselves establish whether differences preceded autism, followed its associated experiences, or reflected another influence. [5]

Hendren and colleagues randomized 57 children to methyl B12 or placebo for eight weeks; 50 completed the trial. Clinician-rated global improvement favored methyl B12, but parent-rated Aberrant Behavior Checklist and Social Responsiveness Scale outcomes did not improve. The discrepancy between measures, small sample, and short follow-up limit broad conclusions. It was an injected methylcobalamin trial, not evidence that all oral B12 or “methylation support” products have the same effect. Neither its response nor nonresponse provides a validated etiologic test. [22]

Common MTHFR polymorphisms do not establish cerebral folate deficiency (CFD), and the AAP does not recommend using them for that diagnosis. [23] A documented nutritional deficiency merits treatment on its own clinical grounds; this should not be represented as proof that a deficiency originally caused ASD. A positive folate-receptor antibody result alone is also not an established diagnosis of FOLR1-related disease.

Folate transport and a specific treatable disorder

FOLR1-related cerebral folate transport deficiency illustrates why a genetic cause and a metabolic treatment are compatible. Pathogenic variants can impair delivery of folate to the brain, producing a neurological disorder that may include autistic features. The original genetic work described a treatable transport defect rather than a general explanation for autism. [6] In March 2026, the FDA approved expanded use of leucovorin calcium (folinic acid) tablets for adult and pediatric patients with confirmed FOLR1-related cerebral folate deficiency. This indication does not extend to autism generally or to a positive folate-receptor antibody test alone. [7]

For broader ASD, Frye and colleagues randomized 48 children with language impairment to folinic acid or placebo for 12 weeks. The between-group improvement in verbal communication was 5.7 standardized points (95% CI 1.0–10.4; Cohen's $d = 0.70$), with a larger estimated effect among folate-receptor-alpha-autoantibody-positive participants. This small, single-site result warrants replication; subgroup findings do not establish a validated population screening strategy. The paper disclosed patent and advisory interests related to antibody testing, reinforcing the value of independent replication. [24]

A separate 2024 folinic-acid trial was retracted in 2026 after concerns about data and statistical analyses could not be resolved. Its results are excluded here as evidence of efficacy. [25] The AAP does not recommend routine leucovorin use for autistic children and emphasizes shared decision-making and monitoring where it is considered. [26] Its clinical FAQ distinguishes CFD assessment from common MTHFR testing and notes uncertainty about benefit without CFD, long-term safety, and reliable selection of responders. Behavioral activation, gastrointestinal effects, and other adverse effects require attention. [23]

Folate availability in the central nervous system should also be distinguished from nonspecific vascular “leakiness.” Transport through the choroid plexus and blood–cerebrospinal-fluid interface is not equivalent to generalized blood–brain barrier breakdown. A transport disorder can limit entry of a needed nutrient without implying that circulating toxins are broadly entering the brain. [6]

Blood brain barrier findings remain preliminary

Fiorentino and colleagues examined postmortem brain tissue from eight ASD donors and reported changes in barrier-associated gene and protein expression. These findings support investigation of neurovascular mechanisms, but postmortem measurements cannot establish when changes arose or whether they caused ASD. Gene-expression changes also are not interchangeable with direct measurement of barrier permeability in living children. [8]

The reported 75% referred to reduced expression of at least one barrier-forming component in 9 of 12 intestinal biopsy samples. It did not mean that 75% of autistic children have a damaged blood–brain barrier. The intestinal barrier, vascular brain barrier, and folate-transport interface must be kept distinct. This study supplies neither a population causal fraction nor evidence for a supplement marketed to “repair the BBB.” [8]

Environmental exposures require agent specific interpretation

Chemical exposure is too broad to be an etiologic category. A defensible assessment specifies the compound, dose, route, developmental timing, and comparison group. Prenatal valproate is an established developmental concern: Christensen and colleagues reported an adjusted ASD hazard ratio of 2.9 (95% CI 1.7 – 4.9) in their overall cohort. However, restricting comparison to children of mothers with epilepsy attenuated the ASD estimate to 1.7 (0.9–3.2).

This matters because the underlying indication can contribute to observed differences. Medication decisions require the prescribing clinician; abruptly stopping antiseizure treatment can create serious risk. [9]

In a California case-control study, residential proximity to reported agricultural pesticide applications was associated with ASD, with odds ratios around 1.10 – 1.16 for several prenatal exposures. Residence-based estimates do not directly measure a child's absorbed dose, and correlated exposures and residual confounding complicate attribution. [10] A US multisite study likewise reported associations that varied by pollutant and developmental window, including third-trimester ozone. These studies do not identify a universal "*chemical autism*" subgroup or establish that removing toxins after diagnosis reverses developmental effects. [11]

Acetaminophen illustrates why study design matters. In the Swedish cohort of 2,480,797 children, a small association in conventional analyses disappeared in sibling comparisons. [12] A 2026 Hong Kong analysis similarly found no association in its sibling-matched ASD cohort of 124,333 children. [13] Sibling methods have limitations, including exposure misclassification and differences between pregnancies, but these results substantially weaken simple causal interpretations of the conventional associations. Neither study supports assigning a percentage of ASD to prenatal acetaminophen.

Vaccines and the evidence against causation

Hviid and colleagues followed 657,461 Danish children and found no increased ASD risk after MMR vaccination, including in examined subgroups with familial or other autism risk factors. The adjusted HR was 0.93 (95% CI 0.85–1.02). This does not imply that vaccination prevents autism; it indicates no detected increased risk under the study model. [14] A separate 2025 Danish cohort of 1,224,176 children found no evidence of increased neurodevelopmental-disorder risk associated with cumulative aluminum exposure from early childhood vaccines; the article has a linked correction. [27] The WHO's 2025 assessment reaffirmed that vaccines, including those containing thiomersal or aluminum, do not cause autism. [15] Accordingly, "vaccine-caused autism" should not be presented alongside established genetic disorders as a plausible treatment category. These conclusions come from substantial comparative evidence, rather than an assumption that every vaccine is incapable of any adverse event. Timing of developmental recognition after vaccination is insufficient to establish causation and does not justify vaccine avoidance or "vaccine detoxification."

Other developmental associations and coexisting conditions

In a Swedish cohort of more than four million people, ASD prevalence was higher after extremely premature than full-term birth; associations persisted with only modest attenuation in sibling analyses. Prematurity nevertheless summarizes many developmental circumstances, rather than identifying a single reversible pathway. [16] Broad maternal-infection associations require similar care: in Brynne and colleagues' sibling comparison, the ASD HR was 0.94 (95% CI 0.82 – 1.08). That result does not rule out effects of every specific infection, but cautions against a universal infection-caused percentage. [17] Microbiome differences also need not identify an initiating cause. Yap and colleagues' study supported a model linking autism-related dietary preferences to reduced dietary diversity and altered microbiome composition. [18] Mitochondrial or other metabolic disorders may warrant investigation when clinical features suggest them, but an abnormal research biomarker is not equivalent to a confirmed disorder. The AAP advises that metabolic testing be guided by history and examination rather than routinely applied to every autistic child. [20]

Translating evidence into individualized care

The most useful treatment target is usually a defined need: communication access, sleep, feeding, constipation, seizures, anxiety, or safety. Developmental, educational, speech-language, and other supports can be individualized without first discovering a single cause. Communication support can include gestures, pictures, or electronic devices as well as speech. Medication can address selected co-occurring symptoms or conditions. [28] Goals should emphasize the child's comfort, agency, participation, and skills rather than the suppression of harmless differences.

Table 2. Interpreting treatment options and lack of benefit

Clinical situation	Reasonable evidence based approach	What nonresponse does not establish
Unmet communication or daily-living needs	Individualized speech-language, educational, developmental, or occupational support; consider augmentative communication. [1,28]	It does not show that the child is incapable of learning or that a biomedical cause must be found first.
Suspected nutritional deficiency or markedly restricted diet	Assess intake, growth, symptoms, and clinically indicated laboratory findings; correct a confirmed deficiency. [20]	It does not exclude every metabolic problem or justify progressively larger supplement combinations.
Confirmed FOLR1-related CFD	Specialist-directed disease-specific treatment and monitoring. [6,7]	It does not make the diagnosis interchangeable with common MTHFR variants or general ASD.
Folinic acid or methyl B12 proposed for ASD without an established indication	Discuss limited trial evidence, risks, alternatives, and whether a monitored trial is justified. Routine leucovorin use is not recommended by the AAP. [22,24,26]	Neither benefit nor failure identifies the original cause; a biochemical change alone is not a functional outcome.
Sleep, gastrointestinal, seizure, or mental-health concerns	Evaluate the specific condition and use appropriate treatment and follow-up. [20,28]	Persistent symptoms do not automatically imply toxins, impaired methylation, or a leaky brain barrier.
General detoxification or barrier-repair claims	Ask for a validated diagnosis and clinical trial evidence. NICE advises against chelation, secretin (peptide hormone), or hyperbaric oxygen as autism treatments. [29]	A claimed mechanism or testimonial does not establish benefit, and failure does not justify escalation.

For a clinician-supervised trial, the family and clinician should agree on the target, a baseline description, expected assessment interval, adverse effects to track, and criteria for continuation or stopping. Keep concurrent changes limited when practical so that improvement can be interpreted. Monitoring might record spontaneous communication, night waking, or pain-related episodes, depending on the actual goal. Necessary treatments should not be withheld merely to make a home comparison cleaner.

When a treatment does not help, reconsider whether it has credible evidence for the chosen outcome, whether the target problem was correctly identified, and whether adverse effects or an untreated coexisting condition are interfering. Persistent deterioration or new loss of skills warrants clinical assessment rather than repeated supplement trials. A negative result may justify stopping an ineffective intervention. It does not create an obligation to keep searching through unproven alternatives.

Discussion

The evidence favors a layered explanation of autism over mutually exclusive causal bins. Genetics can shape developmental pathways; prenatal or early-life exposures may modify risk; biomarkers can be causes, consequences, or correlates; and coexisting disorders can influence function independently of the origins of ASD. A single child can even belong to several of these descriptions. This interpretation reconciles substantial genetic contribution with the possibility of beneficial medical and developmental intervention.

The proposed inference that some parents may be thinking; “*methylation therapy did not help, therefore this child must have genetic or barrier-related autism*” is not supported. A treatment with limited or variable efficacy has poor value as a diagnostic challenge test. Conversely, improvement does not retrospectively establish causation: a treatment could relieve a coexisting problem, affect a downstream pathway, or coincide with maturation or other support. Demonstrating average efficacy in a trial and demonstrating a causal mechanism are separate achievements.

A useful future percentage would require representative recruitment, a reproducible subgroup definition, validated testing, and prospective follow-up. Biomarker-guided care additionally requires randomized evidence showing that marker status predicts a difference in treatment benefit, preferably through a prespecified treatment-by-marker interaction and independent replication. Finding statistical significance in one subgroup but not another is insufficient by itself. Studies should report functional outcomes, adverse effects, uncertainty, and burdens to families, rather than only changes in laboratory measurements.

Limitations

Diagnostic definitions, ascertainment, ancestry, age, exposure measurement, and access to testing differ across studies. Historical diagnostic yields should not be treated as current universal estimates. Small mechanistic studies and short trials have limited generalizability, while observational confounding controls remain imperfect. Evidence may change after the search period. The parent-facing framework is an interpretive synthesis, not a validated diagnostic algorithm or prescribing guideline.

Conclusion

Current evidence cannot support a reliable table allocating all autistic children into percentages caused by genetics, impaired methylation, blood–brain barrier problems, chemicals, and vaccines. While Bai et al. (2019) estimated autism heritability at approximately 80%, indicating that inherited genetic factors account for the majority of population-level variation in autism susceptibility. It can support clearly labeled estimates of heritability, diagnostic yield, exposure-associated risk, and trial outcomes. Families should understand that a treatment’s failure is not their failure and does not reveal an alternative cause. Individualized support, assessment of coexisting conditions, and specific treatment of confirmed disorders offer a more defensible basis for care than a sequence of presumed-cause therapies.

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