ETIOLOGICAL PATHWAYS AND INNOVATIVE APPROACHES TO EARLY AUTISM DETECTION: A CRITICAL NARRATIVE REVIEW

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Abstract

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition arising from interacting genetic, biological, and environmental influences. Earlier recognition can shorten diagnostic delay and enable timely, needs-based support, yet no etiological marker or digital test independently establishes diagnosis.

Objective: To critically integrate evidence on ASD etiology with the clinical performance, readiness, and governance requirements of conventional and technology-assisted early-detection approaches.

Methods: A structured narrative search of PubMed/MEDLINE and authoritative clinical guidance was conducted for English-language publications from 1 January 2014 to 4 September 2026, supplemented by landmark earlier studies. Priority was given to systematic reviews, meta-analyses, large genomic cohorts, prospective diagnostic studies, and guidelines. Evidence was synthesized by etiological domain and technology readiness; causal inference, external validation, calibration, equity, and clinical utility were explicitly appraised. This was not a registered systematic review and no pooled re-analysis was performed.

Results: ASD liability is strongly heritable and polygenic, with additional contribution from rare variants and de novo mutations. Prenatal and perinatal associations—including maternal infection, metabolic conditions, selected medication exposures, prematurity, and parental age—are probabilistic and frequently vulnerable to residual or familial confounding. The M-CHAT(-R/F) remains a scalable first-stage screener; meta-analysis reports pooled sensitivity of 0.83 and specificity of 0.94, with substantial heterogeneity. Artificial intelligence (AI) applied to questionnaires, home video, eye tracking, speech, movement, neurophysiology, and multimodal data can increase objectivity or triage efficiency, but most models require prospective, multisite, demographically representative validation and workflow-impact testing.

Conclusions: The most defensible near-term model is staged, clinician-supervised detection: standardized developmental surveillance and screening, structured follow-up, AI-supported risk stratification when locally validated, and comprehensive diagnostic assessment. Etiological information should guide risk enrichment and counseling—not deterministic labeling. Transparent reporting, bias auditing, privacy protection, and post-deployment monitoring are prerequisites for responsible implementation.

Keywords: autism spectrum disorder; early detection; artificial intelligence; M-CHAT-R/F; genetics; prenatal exposure; digital biomarkers; clinical validation

Highlights

• ASD risk reflects heterogeneous genetic liability interacting with prenatal, perinatal, and developmental contexts.

• M-CHAT-R/F is a screening—not diagnostic—instrument; follow-up interviewing and referral pathways materially affect performance.

• AI is most clinically plausible as an adjunct for triage and measurement, not an autonomous replacement for multidisciplinary diagnosis.

• External validation, calibration, fairness, privacy, and evidence of improved patient pathways should precede deployment.

1. Introduction

Autism spectrum disorder is defined by persistent differences in social communication and interaction together with restricted or repetitive patterns of behavior, interests, or sensory experience, with onset in the developmental period [1]. Clinical expression varies widely across language, cognition, adaptive function, co-occurring conditions, sex, culture, and age [3]. Global prevalence estimates differ across methods and settings, and rising identification cannot be interpreted as a simple increase in biological incidence because diagnostic practice, service access, awareness, and case ascertainment have changed [2–4].

Diagnostic pathways commonly begin after caregivers or professionals recognize developmental differences. Delays are particularly consequential where specialist capacity is limited. Early detection should therefore be understood as a health-system process: surveillance, screening, follow-up, referral, diagnostic assessment, and linkage to individualized support [5,6]. A positive screen estimates elevated likelihood; it does not establish ASD.

1.1 Rationale and contribution

Reviews often treat etiology and detection as separate topics. This review links them through a translational question: which etiological signals can responsibly enrich surveillance, which behavioral or digital measures are mature enough for clinical use, and what safeguards prevent probabilistic associations from becoming deterministic labels? The proposed contribution is an evidence-to-implementation framework that ranks tools by clinical readiness rather than reported accuracy alone.

2. Methods

2.1 Search strategy and eligibility

A structured narrative search was undertaken in PubMed/MEDLINE using combinations of “autism spectrum disorder,” “etiology,” “genetic,” “prenatal,” “perinatal,” “screening,” “M-CHAT-R/F,” “artificial intelligence,” “machine learning,” “eye tracking,” “home video,” “digital biomarker,” and “early diagnosis.” English-language literature published from 1 January 2014 through 4 September 2026 was considered; seminal earlier studies and current WHO, AAP, NICE, and DSM sources were added. Eligible evidence comprised systematic reviews and meta-analyses, large population or genomic cohorts, prospective diagnostic-accuracy studies, and clinical guidance relevant to children. Small proof-of-concept studies were considered only to characterize emerging modalities. Opinion-

only reports, unvalidated commercial claims, and studies without a clinically interpretable reference standard were not used as primary support.

2.2 Synthesis and appraisal

Findings were organized into genetic architecture, prenatal/perinatal correlates, conventional screening, and digital or AI-assisted detection. Appraisal emphasized study design, sample spectrum, reference standard, external validation, calibration, handling of missing data, transportability, and clinical consequences. Because the review was narrative, study selection was not independently duplicated, risk-of-bias instruments were not applied study-by-study, and effect estimates were not re-pooled. Conclusions therefore reflect a critical synthesis rather than a new quantitative meta-analysis.

3. Etiological architecture of ASD

3.1 Genetic liability

Family and population studies demonstrate substantial heritability, but heritability is a population statistic rather than an individual prognosis [7]. ASD genetic architecture includes common polygenic variation, rare inherited variants, copy-number variants, and de novo protein-truncating or damaging missense variants [8–10]. Large exome studies implicate genes affecting neuronal development, synaptic biology, and gene regulation [9]. No single variant explains most cases, penetrance is variable, and many variants are pleiotropic across neurodevelopmental outcomes. Genetic testing may identify an etiological diagnosis in selected patients and inform recurrence counseling or medical surveillance, but it is not a population ASD screening test.

3.2 Prenatal and perinatal factors

Umbrella reviews and meta-analyses report associations between ASD and several prenatal or perinatal conditions, including advanced parental age, maternal infection or fever, diabetes and obesity, certain medication exposures, preterm birth, and neonatal complications [11–14]. These associations typically have modest effect sizes and may reflect correlated genetics, indication bias, socioeconomic factors, healthcare utilization, or shared family environment. Exposure timing and phenotype definitions also vary. Consequently, an association should not be presented as proof that a parent, medication, or single pregnancy event caused a child’s autism.

3.3 Integrative interpretation

A liability-threshold model best accommodates the evidence: many genetic and non-genetic influences alter neurodevelopmental probability, while protective factors, developmental plasticity, and measurement context influence observed phenotype. Etiological data can identify groups warranting closer developmental surveillance—such as younger siblings of autistic children or infants with defined genetic syndromes—but should not trigger irreversible labeling in the absence of developmental evidence [26,29].

Domain	Best-supported inference	Potential use	Major limitation
Common and rare genetic variation	Strong contribution to population liability; heterogeneous pathways	Etiological work-up, recurrence counseling, risk-enriched follow-up	Variable penetrance; limited individual prediction
Maternal metabolic/inflammatory conditions	Replicated observational associations	Optimize maternal care; research stratification	Residual confounding and exposure heterogeneity
Prematurity/neonatal complications	Elevated group-level probability	Enhanced developmental surveillance	Non-specific to ASD; competing neurodevelopmental outcomes
Family history/early developmental trajectory	Clinically meaningful enrichment	Earlier repeated screening and referral	Not deterministic; phenotype changes with age

4. Conventional early detection

Developmental surveillance is longitudinal and integrates caregiver concerns, milestones, observation, and medical context. Standardized screening adds reproducible risk estimation. AAP guidance supports autism-specific screening at 18 and 24 months, while local programs must align timing and referral capacity with population needs [5]. NICE emphasizes recognition of signs, referral, and comprehensive assessment rather than reliance on any single instrument [30].

4.1 M-CHAT-R/F

The M-CHAT-R/F is a two-stage parent-report screener designed for children aged 16–30 months. The initial 20 items are followed, when indicated, by a structured interview that clarifies responses and reduces false positives [15]. In a 2023 systematic review and meta-analysis of 50 studies, pooled sensitivity was 0.83 (95% CI 0.77–0.88) and specificity 0.94 (95% CI 0.89–0.97), but heterogeneity was considerable [16]. Performance varies with language, culture, risk setting, scoring, follow-up completion, verification of screen-negative cases, and age. Thus, pooled values should not be transplanted uncritically into a new health system.

A positive result warrants timely developmental evaluation and referral according to local protocol; it is not a diagnosis. A negative result does not override persistent caregiver

or clinician concern. Fidelity to the follow-up interview, culturally validated translations, repeat surveillance, and tracking of referral completion are core quality indicators [15–17].

5. AI and digital phenotyping

AI can process high-dimensional behavioral or biological data and combine weak signals. Candidate inputs include questionnaire responses, short home videos, gaze trajectories, vocal features, motor patterns, electronic health records, electroencephalography, neuroimaging, and multimodal combinations [18–25]. However, high internal accuracy may reflect dataset artifacts, spectrum restriction, duplicated participants, or leakage between training and test data. Clinically meaningful evaluation requires locked models, external cohorts, transparent thresholds, calibration, subgroup analyses, and comparison with current care.

Modality	Clinical promise	Evidence status	Key barrier
Questionnaire-based ML	Rapid triage; low hardware burden	Multiple retrospective studies; some prospective work	Dataset shift and reduced interpretability
Home-video/computer vision	Remote observation in natural settings	Prospective feasibility and validation reported [18,19]	Video quality, annotation burden, privacy
Eye tracking	Objective social-attention measurement	Prospective diagnostic studies in referred/primary-care samples [20,21]	Equipment, cooperation, spectrum effects
Speech and movement analytics	Passive or brief behavioral markers	Predominantly early-stage heterogeneous studies	Age/language dependence; reproducibility
EEG/neuroimaging AI	Mechanistic and stratification potential	Research-focused; pooled studies show heterogeneity [22]	Cost, sedation/motion, weak generalizability
Multimodal models	May improve robustness and capture heterogeneity	Promising but limited external validation	Missing modalities, complexity, calibration

5.1 From discrimination to clinical utility

Sensitivity, specificity, and area under the receiver-operating-characteristic curve describe discrimination but do not by themselves establish usefulness. Positive predictive value depends on prevalence, and a threshold that is acceptable in a specialist clinic may generate excessive referrals in population screening. Calibration, decision-curve analysis, time to assessment, referral completion, family burden, and developmental outcomes are more relevant implementation endpoints. Comparisons should use the same participants and reference standard, ideally through prospective impact studies.

5.2 Bias, explainability, and safety

Models may underperform in girls, multilingual children, minority populations, children with intellectual or sensory disabilities, and low-resource settings when these groups are underrepresented. Apparent explanations from post-hoc algorithms do not guarantee causal validity. Minimum safeguards include representative recruitment, prespecified subgroup metrics, documentation of missingness, model cards, human oversight, data minimization, secure processing, an appeal pathway, and surveillance for performance drift. Families should know whether AI informs prioritization, screening, or diagnosis and what happens after a positive result.

6. Proposed staged pathway for responsible implementation

Stage	Action	Decision rule	Quality measure
1. Surveillance	Elicit concerns; review milestones and risk context at routine encounters	Concern or elevated risk triggers standardized screening/referral	Coverage and equity by subgroup
2. Standardized screening	Administer validated local-language instrument; complete M-CHAT-R/F follow-up when indicated	Positive screen or persistent concern advances pathway	Follow-up completion; false-negative audit
3. AI-supported triage	Use only a locked, locally validated adjunct on consented data	Prioritizes—not excludes—clinical assessment	Calibration, subgroup sensitivity, override rate
4. Diagnostic assessment	Multidisciplinary history, observation, developmental and medical evaluation	Clinical diagnosis and profile of strengths/needs	Waiting time; diagnostic agreement

5. Support and monitoring	Link family to individualized services; reassess development	Needs-based plan independent of etiological certainty	Referral uptake and family-reported outcomes

This pathway deliberately prevents an algorithmic low-risk result from closing access when developmental concern persists. Etiological assessment and early support can proceed in parallel; neither should be delayed until every diagnostic uncertainty is resolved. In settings with limited specialist capacity, AI may be most valuable for queue prioritization and structured data capture, provided missed-case monitoring is explicit.

7. Research priorities

The next generation of studies should: (1) preregister intended use and thresholds; (2) recruit community-based, multisite cohorts with adequate representation by sex, language, ethnicity, socioeconomic status, and co-occurring disability; (3) separate training, tuning, and external testing at the participant and site levels; (4) report calibration and net benefit alongside discrimination; (5) compare AI-assisted pathways with current care in prospective trials; (6) quantify data and clinician burden; (7) publish negative results and model updates; and (8) involve autistic people and families in outcome selection and governance. Etiological studies should use designs that strengthen causal inference, including sibling comparisons, negative controls, genetically informed methods, and precise exposure timing.

8. Limitations

This narrative review did not use duplicate screening, a registered protocol, formal study-level risk-of-bias scoring, or a new meta-analysis. Restriction to English-language sources may omit relevant regional evidence, including Central Asian validation studies. Rapidly evolving AI literature can also make performance summaries obsolete. The paper therefore supports a translational framework and identifies evidence gaps; it does not endorse a particular commercial product or define a universal clinical threshold.

9. Conclusion

ASD arises through heterogeneous, interacting developmental pathways; neither genetic findings nor prenatal correlates justify deterministic prediction. M-CHAT-R/F remains a pragmatic entry point when administered with its follow-up procedure and embedded in a functioning referral system. AI-enabled behavioral measurement may improve consistency and triage, but reported accuracy is not equivalent to clinical value. A staged, locally validated, clinician-supervised pathway—supported by equity auditing, privacy safeguards, and outcome monitoring—is the most evidence-aligned route to earlier recognition and timely support.

Declarations

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