Review

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Biologically Anchored Digital Biomarkers and Artificial Intelligence for Precision Autism Medicine

Running Title: Biologically Anchored Digital Biomarkers in Autism

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Abstract

Artificial intelligence (AI) has shown promise in autism spectrum disorder (ASD) screening and phenotyping, yet most existing models rely primarily on behavioral signals and lack integration with underlying biological mechanisms. This review proposes a biologically anchored digital biomarker framework that combines behavioral digital phenotyping with key biological systems implicated in ASD, including oxytocin signaling, gut-brain interactions, immune-metabolic regulation, and neurophysiological measures. We highlight emerging evidence from multimodal machine learning, microbiome-informed modeling, EEG-based prediction, and explainable AI to illustrate how integrated approaches may enable biologically meaningful stratification, longitudinal monitoring, and treatment-response prediction. We also discuss implementation considerations for clinical translation, including validation, calibration, dataset shift monitoring, fairness auditing, and clinician-in-the-loop governance. Biologically integrated digital biomarker systems offer a pathway toward precision neurodevelopmental medicine by supporting individualized understanding and intervention beyond categorical diagnosis.

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1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by differences in social communication, restricted interests, repetitive behaviors, and sensory processing. [1] Despite advances in early detection, ASD diagnosis remains largely behaviorally defined, relying on structured instruments and caregiver report, typically operationalized through instruments such as the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). Behavior-based assessment is clinically useful but offers limited insight into biological mechanisms, developmental trajectories, or individualized treatment responsiveness. ASD can be seen as a constellation of neurodevelopmental pathways influenced by genetic, epigenetic, immune-metabolic, and environmental factors. This paradigm shift has increased interest in biomarker-informed precision medicine approaches.

Artificial intelligence (AI) has been widely applied in ASD research using eye tracking, speech analytics, facial recognition, wearable sensors, EEG, and neuroimaging. [2,3] Although many studies report strong classification accuracy, systematic reviews reveal substantial heterogeneity and limited external validation. [4,5] Additionally, many systems lack biological anchoring and operate as black-box classifiers, reducing clinical trust and translational integration. [6]

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In this review, we propose a biologically anchored digital biomarker framework that integrates multimodal biological axes with explainable AI to enable stratification, longitudinal modeling, and treatment-response prediction. We examine how AI can integrate key biological axes to support clinically meaningful decision-making across development, particularly oxytocin signaling, the gut-brain axis, and multimodal biomarkers.

2. Limitations of Behavior-Centered Digital Biomarkers

Most AI-driven ASD studies emphasize behavioral signal extraction, including gaze fixation metrics, vocal prosody, facial affect, and movement signatures. These approaches demonstrate feasibility for early screening, particularly in preschool-aged cohorts. [4,5] However, high classification performance does not equate to clinical utility. Models frequently optimize separation between ASD and typically developing controls without clarifying actionable implications. [6] Boundary phenotypes, compensated individuals, and complex comorbid cases are often poorly captured. Furthermore, categorical classification reinforces static labeling rather than developmental dimensionality.

Generalizability remains a major challenge. Many models rely on curated datasets with limited demographic diversity. This leads to inflated performance estimates when external validation is absent. [7] Without biological integration, digital biomarkers risk being interpreted deterministically rather than probabilistically. These limitations support a shift toward biologically contextualized, longitudinally informed AI systems.

3. Oxytocin Signaling and Social Salience Integration

Oxytocin regulates attachment, social salience, and stress reactivity. Variability in OXTR and CD38 genes, altered endogenous oxytocin levels, and heterogeneous responses to intranasal oxytocin have been observed in subsets of autistic individuals. [8–10] Integrating endocrine markers, autonomic stress indices, and digital social attention measures within AI frameworks may enable identification of biologically responsive subgroups. Latent clustering approaches have successfully identified mechanistically coherent psychiatric subtypes [11] , suggesting feasibility in ASD. Explainable eye-tracking-based AI systems further illustrate how interpretable features can enhance clinical relevance. [12] Rather than predicting categorical diagnosis, biologically informed AI may identify oxytocin-related phenotypes and inform targeted therapeutic strategies.

4. Gut-Brain Axis and Immune-Metabolic Regulation

The gut-brain axis has emerged as a big contributor to neurodevelopmental variability. Altered microbiome composition, immune activation, and microbial metabolites correlate with behavioral outcomes in ASD. [13,14] Machine learning approaches have identified reproducible microbiome signatures across cohorts, although reproducibility varies. [15] Integrative multi-omics analyses combining microbial genomics, metabolomics, and cytokine profiling reveal complex host-microbe interactions associated with ASD phenotypes. [16] These interactions are dynamic and state dependent. AI is well suited to modeling nonlinear host-microbial-immune relationships longitudinally. Reviews of AI-based early autism detection technologies highlight the importance of integrating biological biomarkers with digital phenotyping to enhance predictive validity. [17] By modeling modifiable biological states, AI may enable response prediction to dietary, probiotic, or anti-inflammatory interventions and support state monitoring across development.

5. Multimodal Neurophysiological Biomarkers

Multimodal biomarker integration consistently outperforms unimodal approaches in capturing ASD heterogeneity. [18,19] EEG-based machine learning has expanded rapidly, encompassing resting-state features, evoked potentials, sleep architecture, and multimodal EEG-fNIRS modeling. [20] Benchmark datasets enhance reproducibility and cross-site validation. [21] Pragmatic screening

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pipelines combining caregiver reports with passive digital sensing, including audio and eye tracking, demonstrate feasibility for scalable deployment. [18] Explainable machine learning frameworks further support clinician interpretability. [12] Clinically, multimodal digital biomarkers are most valuable when applied to early risk stratification, trajectory monitoring, and treatment-response evaluation.

6. AI Strategies for Precision Autism Medicine

Precision medicine in ASD requires biologically meaningful subgroup identification and individualized response prediction. Clustering and latent factor models support mechanistic subtype discovery. [11,19] Trajectory modeling estimates future symptom progression, while response modeling treats treatment effects as continuous and context dependent. Explainability is critical to adoption. Interpretable feature attribution enhances clinician trust and facilitates integration into therapeutic decision-making. [12] This biologically anchored digital medicine paradigm aligns with dimensional neurodevelopmental classification frameworks. [22]

7. Clinical Implementation and Governance

Translation of biologically anchored AI systems into practice requires prospective validation across diverse populations. Evaluation metrics should include calibration, decision-curve analysis, and external benchmarking. Continuous monitoring for dataset shifts and performance decay is essential. A physician-in-the-loop framework ensures that AI outputs inform rather than dictate decisions, preserving patient-centered care while leveraging computational insights. Without these operational safeguards, even high-performing models remain research tools rather than clinical decision-support systems. [17] Bias auditing and fairness evaluation are necessary to mitigate health disparities. Physician-in-the-loop governance structures ensure that AI outputs augment rather than replace clinical judgment. Without operational safeguards, AI systems risk remaining research prototypes rather than clinically deployable decision-support tools. When deployed within ethical, transparent, and clinician-supervised systems, AI can enhance individualized care and advance equitable neurodevelopmental medicine.

8. Conclusions

Artificial intelligence holds transformative potential for autism research and care, but its greatest value lies not in automated diagnosis. Behavior-only models, while informative, are insufficient to address ASD's biological heterogeneity and developmental complexity. Biologically anchored AI systems that integrate oxytocin signaling, gut-brain interactions, immune-metabolic processes, and multimodal biomarkers offer a path toward clinically meaningful stratification and precision medicine. When deployed within ethical, clinician-supervised frameworks, such systems can support individualized understanding, guide targeted intervention, and improve long-term outcomes. Reframing AI as a tool for personalized insight rather than categorical classification represents a critical step toward more effective, ethical, and compassionate autism care.

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