International Journal of Contemporary Pediatrics
Vadhavekar N et al. Int J Contemp Pediatr. 2026 Jan;13(1):113-121
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20254195

Review Article

Neurodevelopmental delays: a review on integration between- WES, WGS and AI guided accelerated and precise diagnosis

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Received: 12 November 2025
Revised: 12 December 2025
Accepted: 18 December 2025

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ABSTRACT

Neurodevelopmental delays (NDDs) are a significant public health concern, and their early, accurate diagnosis is crucial for an effective intervention. This comprehensive literature review examines the transformative impact of integrating whole exome sequencing (WES), whole genome sequencing (WGS), and artificial intelligence (AI) into the diagnostic pathway for NDDs. A systematic search was conducted across scholarly databases to synthesize the latest research on the clinical utility, diagnostic yield, and implementation challenges of these technologies. The review confirms that WES and WGS have become indispensable first-tier diagnostic tools, providing a significantly higher diagnostic yield (30-50%) compared to traditional methods by identifying underlying genetic etiologies, including de novo mutations and structural variants. Moreover, the analysis highlights AI's pivotal role in accelerating and enhancing this process, from automating complex genomic data interpretation to enabling earlier clinical diagnosis through the analysis of behavioral, physiological, and electronic health record data. Despite challenges such as cost, inconsistent insurance coverage, and the need for standardized data-sharing, the synergy between genomics and AI is creating a paradigm shift toward a more precise, equitable, and patient-centered model of care. This integration holds immense promise for shortening the diagnostic journey for affected children and profoundly improving their long-term developmental trajectories.

Keywords: Artificial intelligence, Attention-deficit/hyperactivity disorder, Autism spectrum disorder, Intellectual disability, Neurodevelopmental delays, Whole exome sequencing, Whole genome sequencing

INTRODUCTION

Neurodevelopmental delays (NDDs) are a broad range of conditions that involve disruption of normal brain development and function, resulting in impairments in cognition, behavior, language, and motor skills.[1] Some of the most common NDDs include intellectual disability, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and global developmental delay (GDD).[1] Affected children often miss expected developmental milestones, and the consequences can affect multiple areas such as learning, social interaction, communication, and physical coordination. The prevalence of neurodevelopmental disorders has been steadily rising. In the United States, approximately 8.56% of children aged 3-17 years have

been diagnosed with a developmental disability.[3] These disorders are also a source of considerable strain on families, healthcare systems, and society.[2] Standard diagnostic procedures like clinical evaluation, neuroimaging, and targeted genetic tests usually do not yield conclusive results. This diagnostic uncertainty may delay interventions and affect prognosis.[4] Early identification and intervention have been strongly linked to better outcomes and improved quality of life.[5] With this in mind, advances in genetic testing technologies have transformed the diagnostic approach for neurodevelopmental disorders. WES, which focuses on the protein-coding regions of the genome (about 1%), has emerged as a useful tool.[6] WES has shown diagnostic yields ranging from 20-41% depending on the clinical presentation and patient selection. It is especially effective at identifying de novo mutations, which are a major cause of many neurodevelopmental conditions.[7-9]

WGS is a more comprehensive approach, as it analyzes both coding and non-coding regions of the genome.[10] WGS also detects structural changes and copy number variations that may be missed by WES. Diagnostic yields with WGS were reported to be around 30% in patients with neurodevelopmental disorders.[11] In recent years, AI has played a valuable role in genomic medicine. AI tools can analyze large datasets to identify potential disease-causing genes, predict whether genetic variants are harmful, and prioritize which genes to investigate further. These algorithms have shown strong performance in identifying risk genes for ASD and other developmental conditions.[12]

Despite these advances, challenges include bringing these technologies into everyday clinical practice, interpreting variants of uncertain significance, the need for functional validation, data management, high costs, and a shortage of trained personnel.[13] Other barriers include inconsistent insurance coverage, lack of standard reporting protocols, and limited data-sharing across institutions. Still, studies show that genomic sequencing can ultimately reduce healthcare costs by enabling earlier diagnosis and more targeted care.[14] The success of sequencing also depends on the choice of patients, the complexity of their symptoms, and the type of sequencing performed. Moving forward, improvements in long-read sequencing, single-cell genomics, and proteomics, integrating enhanced AI models capable of integrating clinical and multiomic data, show promise in further advancing the field.

This review explores how combining WES, WGS, and AI can transform early diagnosis of NDDs, discussing current evidence, barriers, and future directions.

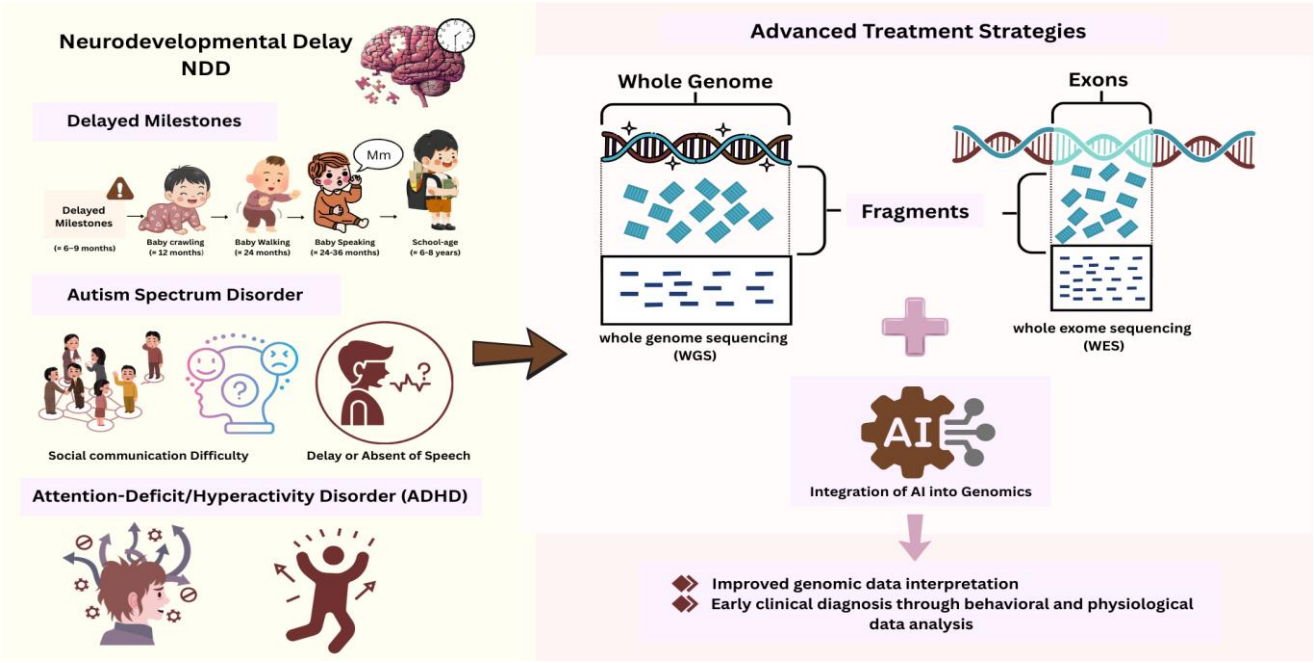

Figure 1: Genomic and AI Strategies for Neurodevelopmental Delay (NDD) Diagnosis.[1,2,10-12]

WES

WES has transformed the genetic evaluation of neurodevelopmental disorders by targeting all protein-coding regions- about 1-2% of the genome- while identifying approximately 85% of disease-causing mutations. Exonic DNA is enriched and sequenced using high-yield platforms, enabling analysis of thousands of genes in a single assay. WES detects single-nucleotide variants, small insertions/deletions, and some copy-number variants within a unified test. Trio sequencing-analysing the affected child alongside both parents-enhances the approach's power by revealing de novo variants, common drivers of early-onset neurodevelopmental conditions.

Researchers in a study validated WES as a first-line tool in developmental and epileptic encephalopathies, finding

pathogenic variants in 43% of children and enabling targeted interventions while eliminating unnecessary invasive and sequential testing.[15] In a study conducted by Sánchez Suárez et al. evaluated 176 Spanish children with ASD, ID, or global delay using WES paired with phenotype-driven panels; trio analysis raised diagnostic yield from 12.5% to 17.1%, reclassifying several uncertain variants.[9] Arteche-López et al. demonstrated that WES alone effectively replaced chromosomal microarray and fragile X testing in autism, optimizing diagnostic processes.[16]

Expanding use into prenatal settings, Lei et al. used WES to identify PPP2R1A pathogenic variants in foetuses with brain anomalies, enabling prenatal counselling and perinatal management.[17] Wu et al applied trio-based WES to Chinese children with neurodevelopmental delay and comorbid epilepsy or ASD, capturing both SNVs and CNVs, and showing the importance of detailed phenotyping.[18] Srivastava et al.'s 2019 consensus supported WES as a first-tier test, pointing to diagnostic yields above 30%, shorter timelines, and cost benefits.[19]

Stoyanova et al. showed that systematic phenotyping and periodic reanalysis of WES data increased diagnostic yield over time.[20] Ko and Chen reviewed global sequencing modalities and concluded that WES balances diagnostic coverage, utility, and cost effectively in clinical settings.[21] Shchubelka et al illustrated in Ukrainian children that WES not only revealed common disease genes but also population-specific variants- highlighting the need for region-specific genomic databases.[22]

Xu et al performed WES in 280 Chinese children with unexplained delay, achieving ~40% diagnostic yield, demonstrating scalability.[23] Alotibi et al compared chromosomal microarray with WES, finding the latter had a substantially higher yield (~30% vs ~16%) and recommending it for first-tier testing.[24] Boyarchuk et al corroborated these findings, diagnosing about one-third of children in their cohort.[25]

Seo et al implemented an automated, daily-update pipeline for exome variant interpretation, reducing turnaround times and maintaining diagnostic currency.[26] Rosina et al presented a prospective Italian study showing that first-tier WES outperformed traditional multistep pathways- faster, more accurate, and cost-effective- while reducing family burden.[27] Stefanski et al meta-analysis across ASD, epilepsy, and ID confirmed diagnostic yields of 25-40% and noted practical impacts on clinical care, especially in epilepsy.[28] Kim et al. emphasized WES's ability to identify rare yet treatable neurologic disorders, enabling earlier intervention.[29]

Collectively, these studies demonstrate that WES delivers comprehensive diagnostic coverage-capturing SNVs and CNVs, especially with trio design- and achieves diagnostic yields frequently between 30% and 50%, which consistently outperform older testing methods like chromosomal microarray.[24,28] WES not only accelerates diagnosis but also directly informs precision interventions, including antiseizure medication decisions, metabolic therapies, and prenatal planning.[9,29] Technological improvements- such as automated pipelines, systematic reanalysis, and enriched regional databases- ensure genomic data remains clinically relevant across diverse global populations.[22,26,29]

Despite its strengths, WES still faces challenges in interpreting variants of uncertain significance and in detecting non-exonic or structural genomic alterations- gaps that can be addressed through enhanced bioinformatics, complementary testing, and consented re-analysis.[24,29] Ethical considerations, including protocols for incidental findings and informed consent processes, must also be integrated through interdisciplinary teams to ensure responsible, patient-cantered implementation.[19,27]

In conclusion, WES has established itself as the cornerstone of neurodevelopmental genetics, offering unmatched diagnostic depth, precision, and clinical impact. The various studies, spanning clinical cohorts, prenatal applications, workflow innovations, and global analyses, collectively validate WES as the definitive first-tier diagnostic test for paediatric neurodevelopmental disorders, heralding a new era of personalized genomic medicine.

WGS

Genome sequencing is a genetic test that has superseded traditional diagnostic tests, such as chromosomal microarrays and next-generation sequencing. It is divided into pre-sequencing, sequencing, and post-sequencing stages and can detect all variations in the DNA within the genome.[31]

The practical application of WGS is in its utility as a diagnostic tool whose yield can vary from a few percent in the detection of respiratory or hematological disorders to 40-50 percent for neurodevelopmental disorders.[32] The neurodevelopmental disorders develop due to a variety of genetic causes and present in the form of cognitive disorders, seizures, and movement disorders. Thus, WGS not only helps in the detection of these etiologies but is also beneficial in risk counselling and further precision-based management.[33]

Multiple studies have been conducted that demonstrate the applicability of whole genome sequencing for disorders like neurodevelopmental delay. A study conducted at the American University of Beirut Medical Center identified that the diagnostic yield of WGS was 57.1% in patients with refractory epilepsy and neurodevelopmental delay. This improved the control of seizures, thereby delivering targeted management.[34] The detection of de novo genomic alterations has led to the determination of the pathogenesis of various diseases that are less described in the literature. Regarding this, a de novo heterozygous transient receptor

potential cation channel subfamily M (melastatin) member 3 (*TRPM3*) missense variant, p.(Asn1126Asp), was identified in a patient with cerebral palsy and developmental delay using WGS.[35] Similarly, another study conducted in Zagreb utilised a trio WGS analysis to detect a de novo nonsense variant AGO3 and KHSRP in a patient with Global developmental delay and autistic features.[36] The usefulness of WGS has also been demonstrated in a preclinical study where bi-allelic truncating variants in AMFR have been identified in patients with Hereditary Spastic Paraplegia, by altering lipid metabolism. In this way, precision medicine allows clinicians to tailor statin treatment based on the individual genetic profiles.[37]

Many studies have identified whole genome screening as not only a promising screening strategy, especially for newborns, but also as a path towards precise genetic diagnosis (PrGD). However, due to various social and ethnic disparities the access to these genetic tests is limited, thereby leading to a diagnostic odyssey (the path towards diagnosis of the disease). Influenced by such disparities, an initiative named SeqFirst was launched to expand the accessibility of whole genome sequencing across diverse communities. It tested the genotype-driven service delivery models in pediatric care settings.[38]

Recent trends reveal that the U.S accounted for 46.3% of the global whole genome sequencing market until 2024, which is expected to lead by 2030. In contrast, Canada is one of the fastest-growing regional markets in North America and can reach up to USD 342.5 million by 2030.[39] Canada runs ahead in this sector, with evolving projects in the field of translational genomics like Care4Rare Canada, the CAUSES Clinic at BC Children's Hospital, the Integrated Centre for Pediatric Clinical Genomics in Montréal, the Silent Genomes Project, and Genome Canada's All-for-One initiative.[40] Likewise, the United Kingdom National Health Service (NHS) is one of the first national healthcare systems in the world that offers WGS for rare disease diagnosis as part of routine care. They have promoted 'mainstreaming', that is, allowing genomic testing to be requested by non-genetic medical specialists (pediatricians as well). However, only 49% of the pediatricians who were surveyed in England recently felt prepared for mainstreaming.[41]

Additionally, other countries like Japan launched the WGS project, "The Action Plan for Whole Genome Analysis for Cancer and Rare/intractable Diseases" in 2019, which utilised the high-quality national genomic data to promote personalised medical care and research.[42]

AI

Since 2021, the American College of Medical Genetics and Genomics (ACMG) has advocated for the use of WES and WGS as frontline tests for children presenting with congenital anomalies, global developmental delays, or intellectual disability.[43]

While approximately 80% of variants causing Mendelian disease are located within the exome, making whole-exome sequencing an attractive method for identifying genetic causes of neurodevelopmental conditions, the diagnostic yield of WES is only 30-50% among patients with mild to severe neurodevelopmental delay/intellectual disability.[44,45]

A major limitation is the complexity of interpreting sequencing data, especially for missense variants, non-coding regions, and structural anomalies. Traditional interpretation methods are time-intensive and rely heavily on manual categorization by expert geneticists, which is unsustainable for large-scale or real-time clinical implementation.

AI offers novel solutions to overcome these limitations by improving both genomic data interpretation and early clinical diagnosis through behavioral and physiological data analysis. AI-guided diagnostic platforms have demonstrated high performance in both controlled and real-world settings, outperforming traditional methods in speed, accuracy, and scalability.

A range of AI technologies has been integrated into diagnostic workflows, including gradient-boosted decision trees, digital phenotyping tools, multi-modular machine learning (ML) systems, and AI-enhanced clinical decision support platforms.

Megerian et al used a gradient boosted decision tree machine learning algorithm to produce either an ASD positive, ASD negative, or indeterminate output, and compared it with agreement of diagnosis between independent specialists. It reported a mean diagnosis age for ASD of 2.81 years using AI tools, which is 1.5 years earlier than conventional practices.[46]

Perochon et al demonstrated a rapid median time of 3.5 months from screening to evaluation of ASD, using a digital phenotyping application, which is a similar or shorter duration compared to real-world settings. These advancements not only improve diagnostic accuracy but also enable timely access to early intervention services, which are critical for improving long-term developmental outcomes.[47]

The interpretation of genomic variants represents one of the most challenging aspects of genetic diagnosis, particularly for missense variants and non-coding regions. Machine learning models have begun to automate variant classification and predict pathogenicity with increasing accuracy.[48]

For example, The Human Splicing Code is one of the first AI tools that used Bayesian models to predict splicing disruptions from triplet exons. It successfully identified pathogenic intronic and missense mutations, such as those implicated in ASD and spinal muscular atrophy, enhancing diagnostic yield from WES data.[49]

DeepSEA, a deep learning algorithm, further expands this capability by predicting non-coding variant effects using chromatin profiling data, such as DNase I sensitivity, transcription factor binding, and histone modification patterns.[50]

Beyond static genetic data, AI has also shown promise in analyzing neurophysiological signals. EEG-based machine learning models achieve 85-97% accuracy by analyzing connectivity, event-related potentials, and oscillatory patterns. These systems are non-invasive, low-cost, and well-suited for pediatric and low-resource settings.[51-53]

One study developed a convolutional neural network (CNN) model that classified children with and without ADHD based on EEG images, with 90.29% accuracy. Their method used a new way to represent EEG data, making it suitable for CNN analysis and allowing detection of personalized brain activity patterns. This could help identify specific neural features in children with ADHD and support more targeted treatment planning.[54] Similarly, another study used multiple support vector machine (SVM) classifiers trained on EEG power spectra to classify adult ADHD subtypes, achieving accuracies between 87.5-95% across various testing conditions (eyes closed, eyes open, VCPT and ECPT).[55]

AI has also been applied to electronic health records (EHRs) for early diagnostic prediction. A large-scale study in Wisconsin used EHR data from over one million individuals to develop an AI model for Fragile X syndrome. The system identified cases with around 80% accuracy and detected them at least five years earlier than traditional methods without using genetic or familial data. However, its findings were primarily generalizable to males diagnosed during the second decade of life.[56] Similarly, deep neural network models have been used for first-trimester screening of Down syndrome, achieving AUC scores as high as 0.96.[57]

AI-based tools have also been instrumental in accelerating behavioral and physiological diagnostics. For example, a video-based system using gradient-boosted decision trees to analyze videos and caregiver questionnaires has demonstrated 98.4% sensitivity and 78.9% specificity in diagnosing ASD.[46] Building on this, another multi-modular AI model that combines video, clinician, and parent inputs, again to diagnose ASD, reporting AUC values as high as 0.92 and with sensitivity and specificity up to 90% and 83%.[58]

Further expanding diagnostic capabilities, the SenseToKnow app integrated video, eye tracking, touch interaction, and behavioral features such as blink rate and social attention to diagnose autism combined with XGBoost algorithms to achieve 87.8% sensitivity and 80.8% specificity, negative predictive value=97.8% and positive predictive value=40.6%, all within primary care workflows.[47]

Beyond ASD, multimodal platforms have demonstrated broader applicability across neurodevelopmental conditions. A large-scale AI platform that combined EHR, wearable device data, and clinical checklists demonstrated 91% diagnostic accuracy for neurodevelopmental disorders in a dataset of over 20,000 children.[59] Additionally, AI-enhanced video analysis has shown promise in the context of standardized developmental assessments. One such study applied the YOLOv5 model to evaluate infant performance on the Bayley Scales of Infant Development. The model achieved 86.5% sensitivity and 100% specificity for the “Places Pegs In” task and 96.9% sensitivity and 89.5% specificity for the “Blue Board” task, highlighting the precision with which AI can capture subtle motor and cognitive behaviors in early development.[60] Motion analysis from video recordings has also been used to detect early signs of cerebral palsy.[61] Speech-based NLP tools, analyzing linguistic and acoustic features, have reached 87% accuracy in identifying communication disorders and ASD, making them ideal for mobile-based screening.[62]

Successful implementation of AI tools requires seamless integration into existing care pathways. These tools have been shown to reduce time demands compared to traditional assessments, making them suitable for primary care environments.[46] They can be used by general pediatricians with remote specialist support, offering a scalable approach to early diagnosis.[63] Clinicians and caregivers have also reported that the tools are easy to use and add value to the diagnostic process.[64]

Importantly, these systems maintained consistent diagnostic performance across diverse demographic subgroups. In contrast to other tools like M-CHAT/F, which showed a positive predictive value (PPV) of 14.6% and lower accuracy for girls and children of color, newer AI tools achieved PPVs of 40.6% and demonstrated equitable performance regardless of sex, race, or socioeconomic background.[46,47,65] However, studies reporting on downstream intervention timelines and long-term outcomes is limited. Future research should prioritize evaluating how early AI-facilitated diagnosis translates to improved developmental trajectories and health equity.

Table 1: Genomic and AI technologies for neurodevelopmental diagnosis: features, applications, and limitations.

Technology	Key Features	Clinical Applications	Limitations
WES	• Targets all protein-coding regions (~1–2% of genome)[15]	• First-line tool in developmental and epileptic encephalopathies[15]	• Variants of uncertain significance[24,29]

Continued.

Technology	Key Features	Clinical Applications	Limitations
	• Captures ~85% of disease-causing mutations[15] • Detects SNVs, small indels, and some CNVs[24,28] • Trio sequencing enhances de novo variant detection[15]	• Improved yield with trio analysis[9] • Replaced chromosomal microarray and fragile X testing in autism[16] • Prenatal detection of PPP2R1A variants[17] • Faster, more accurate, cost-effective; reduces family burden[19,27,28]	• Misses non-exonic and structural alterations[24,29] • Ethical concerns (incidental findings, consent)[19,27] • Requires periodic reanalysis and regional genomic databases[20]
WGS	• Analyzes coding and non-coding regions[10] • Detects structural changes and CNVs missed by WES[11] • Involves pre sequencing, and post sequencing stages[31]	• Identified de novo TRPM3 variant (cerebral palsy + delay)[35] • Identified de novo AGO3 and KHSRP variants (global delay + autistic features)[36] • Identified AMFR variants (Hereditary Spastic Paraplegia, guided statin therapy)[37] • Used in newborn screening[38] • Implemented in SeqFirst, NHS, Japan's Action Plan[38]	• Limited access due to social and ethnic disparities[38] • High cost[13] • Need for trained personnel[13] • Mainstreaming challenges (only 49% pediatricians in England felt prepared)[41]
AI	• Improves genomic data interpretation[46] • Enables early diagnosis from behavioral, physiological, and EHR data[46] • Outperforms traditional methods in speed, accuracy, scalability[46]	• Enables earlier ASD diagnosis[63] • Shortens screening to evaluation time[47] • Automates variant classification (Human Splicing Code, DeepSEA)[48] • Analyzes neurophysiological signals, video-based behavior, and speech features[46,51,52,53] • Usable in primary care[46,47] • Consistent performance across diverse groups[46,47,65]	• Complexity of variant interpretation[48] • Few studies on long term outcomes • Need to assess impact on developmental trajectories and health equity

CONCLUSION

Over the past decade, genetic technologies have transformed our ability to diagnose neurodevelopmental delays more accurately and earlier in life, among which WES and WGS have emerged as essential tools in the diagnostic pathway. While traditional diagnostic methods have long served as the foundation of clinical practice, WES and WGS have emerged as indispensable tools, offering a significantly higher diagnostic yield by identifying the underlying genetic etiologies of NDDs. WES, provides a rapid and cost-effective approach to pinpointing mutations in protein-coding regions, while WGS offers a more exhaustive view of the entire genome, capturing a wider array of genetic variants often missed by other methods. Together, these methods represent a fundamental shift from traditional stepwise genetic testing toward comprehensive, first-line genomic analysis. Trio sequencing, periodic reanalysis, and region-specific genomic databases have further improved their diagnostic power. Moreover, the inclusion of these technologies in prenatal and neonatal care highlights their role in early detection and prevention. In conclusion, alongside genomic technologies AI has emerged as a powerful complement to traditional genetic testing. Machine learning models have demonstrated impressive accuracy in diagnosing autism spectrum disorder, attention-deficit hyperactivity disorder, and other developmental conditions, often years earlier than conventional approaches. Taken together, WES, WGS, and AI-guided approaches are redefining the field of neurodevelopmental medicine. By enabling early and accurate diagnoses, they open the door to timely interventions, improved quality of life, and reduced long-term healthcare costs. These tools provide unprecedented depth, speed, and accuracy, and they hold the potential to transform patient outcomes on a

global scale. Continued investment in research, infrastructure, and equitable access will ensure that the benefits of these technologies reach every child affected by neurodevelopmental delay, ushering in a new era of personalized and precise care. The future of NDD diagnostics lies in this powerful synergy, creating a new era of genomic medicine where precision and early action are the standard of care.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Vadhavekar N, Walia S, Misra G, Palakodeti S, Kankariya S, Pandya M, et al. Neurodevelopmental delays: a review on integration between- WES, WGS and AI guided accelerated and precise diagnosis. Int J Contemp Pediatr 2026;13:113-21.