Jordan Journal of Pharmaceutical Sciences, Volume 17, No. 3, 2024

Integrating Artificial Intelligence and Advanced Genomic Technologies in Unraveling Autism Spectrum Disorder and Gastrointestinal Comorbidities: A Multidisciplinary Approach to Precision Medicine

Lama Ghunaim[1], Ahmed S.A. Ali Agha[2], Talal Aburjai[*2]

[1] Faculty of Educational Sciences, Department of Counseling and Special Education. The University of Jordan. Amman, Jordan.
[2] School of Pharmacy, Department of Pharmaceutical Sciences. The University of Jordan. Amman -Jordan.

ABSTRACT

This article explores the potential impact of Artificial Intelligence (AI), Machine Learning (ML), CRISPR-Cas9 gene editing, and single-cell RNA sequencing on improving our understanding and management of Autism Spectrum Disorder (ASD) and its gastrointestinal (GI) comorbidities. It examines how these technologies illuminate the complex interplay between the gut and the brain, identifying specific enzyme deficiencies and microbial imbalances linked to GI symptoms in ASD. By leveraging AI and ML, personalized intervention strategies are developed through the analysis of genomic, proteomic, and environmental data, enhancing our ability to predict and address GI issues in ASD. Additionally, CRISPR-Cas9 gene editing holds promise for correcting genetic abnormalities related to enzyme production, potentially offering precise treatments. Single-cell RNA sequencing provides critical insights into the cellular diversity of the ASD gut, uncovering new therapeutic targets. The article highlights the transformative potential of these technologies while addressing the associated challenges and ethical considerations. It underscores the necessity of a multidisciplinary approach to fully harness their benefits and discusses the significant progress and emerging trends in the field, emphasizing the role of technological advancements in advancing precision medicine for ASD and its GI comorbidities.

Keywords: Autism Spectrum Disorders; Enzymatic Dysfunction; Dietary Interventions; Gastrointestinal Comorbidities; Personalized Nutrition Therapy.

INTRODUCTION:

Autism Spectrum Disorder (ASD) and its gastrointestinal (GI) comorbidities present significant healthcare challenges [1-3], affecting a large number of individuals worldwide. Recent advancements in Artificial Intelligence (AI), Machine Learning (ML), CRISPR-Cas9 gene editing, and single-cell RNA sequencing mark a notable progression in precision medicine [4, 5]. These technologies enhance our understanding and management of these complex conditions. This article offers a comprehensive analysis of how these innovations contribute to elucidating the intricate relationship between the gut and the brain in individuals with ASD, as illustrated in Figure 1.

[*]***Corresponding author: Talal Aburjai***
aburjai@ju.edu.jo
Received: 19/02/2024 Accepted: 04/04/2024.
DOI: https://doi.org/10.35516/jjps.v17i3.2410

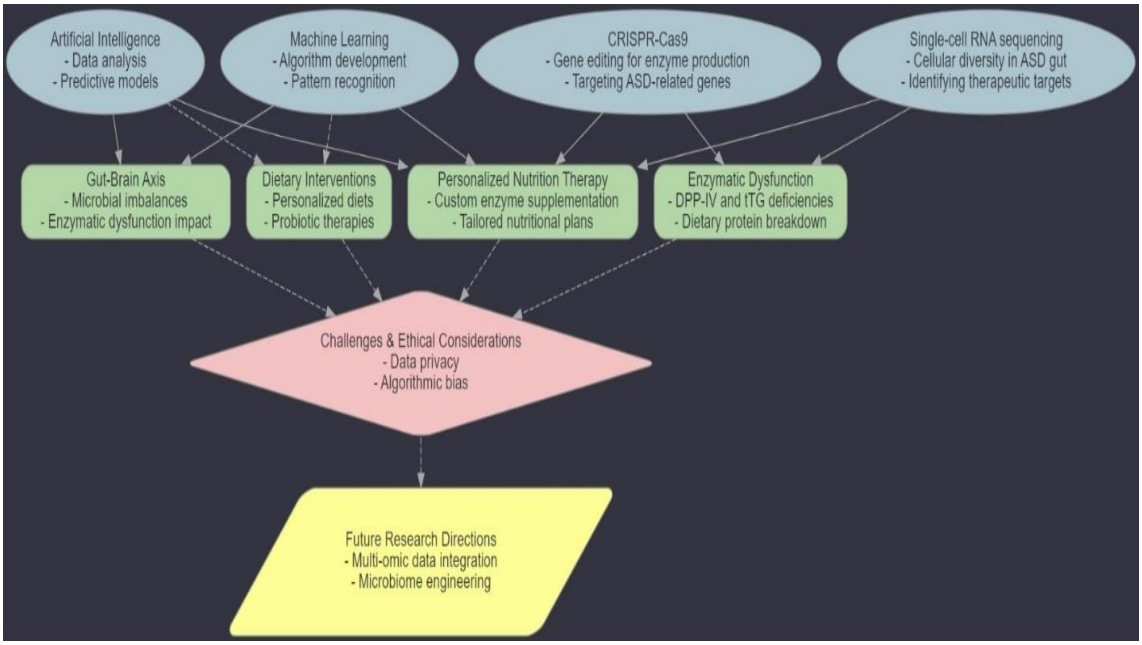

Figure 1 Role of various technologies in understanding the complex relationship between the gut and the brain in individuals with Autism Spectrum Disorder.

It highlights key findings related to specific enzyme deficiencies and microbial imbalances associated with GI symptoms in patients with ASD. The use of AI and ML to analyze genomic, proteomic, and environmental data has led to the development of personalized intervention strategies tailored to the unique characteristics of individuals with ASD. The effectiveness of these interventions hinges on a deep understanding of the genetic and cellular mechanisms underlying ASD, which is facilitated by CRISPR-Cas9 and single-cell technologies. This review offers a comprehensive analysis of recent advancements, addresses the challenges encountered in translational research, and proposes potential future directions. These advanced technologies hold the promise of transforming diagnostic and therapeutic approaches, offering customized solutions that extend beyond conventional methods, as illustrated in Figure 2.

This review aims to provide a critical analysis of technological advancements in the study of ASD and GI comorbidities. It advocates for the continued exploration and application of AI, ML, and genetic technologies. Collaborative efforts from various scientific disciplines are necessary to address the remaining challenges and fully leverage these technologies to improve patient care in ASD.

Autism and Gastrointestinal (GI) Comorbidities

The integration of AI and ML into the diagnosis of ASD and GI disturbances has marked a significant shift towards precision medicine [4]. AI and ML methodologies focus on creating and utilizing algorithms capable of learning from data to make predictions or decisions. AI models are developed using extensive datasets that include genomic, proteomic, and environmental information to study the relationship between ASD and GI comorbidities [6, 7]. These models use supervised learning to recognize patterns and connections between genetic markers or environmental factors and the occurrence or intensity of ASD and its associated GI symptoms [8, 9]. ML methods, including deep learning, are particularly valuable for analyzing complex, multi-dimensional data, enabling the discovery of subtle biomarkers and risk factors that might elude human analysts [10-12].

Figure 2 Illustrating the integration of AI, ML, CRISPR-Cas9, and single-cell RNA sequencing in advancing the understanding and treatment of Autism Spectrum Disorder (ASD) and its gastrointestinal (GI) comorbidities, highlighting the pathway from technological advancements to personalized interventions.

These technologies have elucidated the complex interplay between neurological development and GI health, identifying key enzymatic and microbial factors underlying ASD-related GI symptoms [7, 13]. By analyzing enzyme activity profiles and gut microbiota composition with enhanced precision, AI and ML are uncovering specific enzyme deficiencies that impair the breakdown of dietary proteins such as gluten and casein in individuals with ASD [14, 15], leading to the accumulation of neuroactive peptides. Advanced AI models utilize genomic and proteomic data to identify enzyme gene expressions linked to these digestive inefficiencies [6, 7]. ML algorithms also map changes in gut microbiota, highlighting microbial imbalances that exacerbate GI symptoms and influence neurodevelopment through the gut-brain axis [16]. These models provide predictive insights, enabling the identification of individuals at risk for specific GI conditions and the development of targeted interventions.

Innovative applications extend to predictive algorithms that integrate clinical, genomic, and environmental data to forecast the emergence of GI symptoms, facilitating early intervention. For example, ML analyses of stool samples have identified microbial signatures predictive of constipation in ASD [16], guiding the development of personalized probiotic therapies. AI and ML have greatly improved our understanding and management of ASD and its related GI comorbidities. Through the application of these technologies in examining clinical, genomic, and environmental data, we have successfully predicted GI symptoms and tailored interventions for individuals with ASD. Table 1 presents the predictive insights from AI and ML analyses, underscoring their crucial role in developing targeted therapeutic strategies.

Table 1 AI and ML Predictive Outcomes for ASD Interventions. Summarizes predictive outcomes based on clinical, genomic, and environmental data, their implications for tailored ASD interventions.

Data Type	Predictive Outcome	Implications for Intervention	References
Clinical	Assessing the Risk of GI Conditions in ASD	Early, personalized interventions improving outcomes.	[17]
Genomic	GI symptom emergence based on ASD genetic profiles	Genetically tailored dietary and therapeutic strategies.	[18]
Environmental	GI symptom triggers in ASD from environmental factors	Custom environmental management to mitigate symptoms.	[19]
Clinical + Genomic	ASD diagnosis/prognosis and GI disturbances prediction	Timely, integrated interventions for ASD and GI health.	[20]
Genomic + Environmental	Enzyme deficiencies and microbial imbalances risk in ASD	Proactive diet and lifestyle management for ASD GI health.	[21]
Multifaceted (Clinical, Genomic, Environmental)	Personalized therapy outcomes for ASD, including dietary and probiotic efficacy	Precision care plans optimizing dietary and therapeutic interventions.	[22]

Furthermore, the application of AI and ML extends beyond diagnostic and therapeutic interventions to include genetic editing insights from CRISPR-Cas9 and cellular-level understanding through single-cell RNA sequencing, offering a comprehensive view of the ASD-GI connection [23-26]. This approach enhances the potential for personalized care, leveraging in-depth knowledge of individual enzymatic and microbial profiles to customize dietary and therapeutic strategies, thereby improving the quality of life for individuals with ASD.

Enzymatic Mechanisms in ASD

Research into ASD and its associated enzymatic dysfunctions is being advanced through the integration of AI and ML technologies [7]. This integration is leading to significant progress in understanding the complexities of ASD. These new methods are improving our knowledge of the genetic and microbial factors that affect enzyme activity and are paving the way for the development of new interventions and diagnostic tools. A notable development is the use of AI algorithms to analyze outcomes from CRISPR-Cas9 gene editing experiments that target genes involved in enzyme production essential for ASD [27]. CRISPR-Cas9 gene editing is a highly accurate and adaptable method for making specific changes to the DNA of organisms [28]. The technique involves creating a short RNA sequence (guide RNA) that corresponds to the DNA sequence intended for editing [29]. The Cas9 enzyme, guided by the RNA molecule, cleaves the DNA at a precise location, enabling the modification of DNA sequences [30]. CRISPR-Cas9 is used

in ASD research to correct or introduce mutations in genes linked to enzymatic production or regulation [31]. This helps understand the genetic basis of ASD and GI comorbidities and facilitates the creation of therapeutic approaches.

Additionally, single-cell RNA sequencing (scRNA-seq) is an effective technique for examining the gene expression patterns of individual cells [32]. The process involves isolating single cells, reverse-transcribing their RNA into cDNA, and sequencing the cDNA to identify RNA molecules in each cell [33]. By analyzing profiles from numerous cells of individuals with ASD, scRNA-seq enables researchers to reveal variations in cells within the GI tract and brain [34], identify distinct cell types and states related to the disorder, and find novel targets for treatment.

By simulating genetic alterations in enzyme activity, researchers can investigate gene therapy strategies to address the underlying causes of digestive and neurological symptoms associated with ASD. Modifying genes related to the production of dipeptidyl peptidase-IV (DPP-IV) has the potential to enhance the metabolic breakdown of gluten and casein [35], thereby reducing their adverse effects on individuals with ASD. This thorough mapping enables the identification of specific cell types involved in enzymatic dysfunctions and abnormal gut permeability [36]. Accurate identification of cellular targets for therapeutic intervention has the potential to restore gut health and alleviate symptoms associated with ASD [37]. In the field of metabolomics, AI and ML models are being used to analyze the metabolic pathways affected in the gut microbiome of individuals with ASD [7, 38]. These models identify specific metabolic signatures linked to enzyme deficiencies, guiding the development of targeted interventions such as dietary modifications, supplements, or microbiome engineering. This approach aims to restore equilibrium to metabolic pathways, thereby mitigating the GI and behavioral symptoms associated with ASD.

In addition, AI is being used in therapeutic interventions, such as the creation of virtual reality (VR) platforms that replicate social interactions for individuals with ASD [39, 40]. These AI-driven VR systems dynamically adjust to users' reactions, offering personalized behavioral therapy to improve social skills and alleviate anxiety. Moreover, AI is transforming ASD diagnostics by utilizing tools that analyze intricate patterns in behavior, genetics, and facial expressions [41]. The goal of these tools is to identify ASD at an early stage, as shown in Figure 3.

Allowing for prompt interventions in dietary management and therapy, this has the potential to mitigate the severity of symptoms associated with enzymatic dysfunctions.

Gluten, Casein, and Enzymatic Dysfunction: Evidence and Insights

In the field of ASD research, the integration of AI and ML, along with CRISPR-Cas9 gene editing, scRNA-seq, metabolomics, microbiome analysis, and VR interventions, has significantly improved our understanding and approaches to managing the enzymatic digestion of dietary proteins like gluten and casein [42-44]. The utilization of AI and ML technologies has played a crucial role in analyzing the intricate genetic and biochemical aspects linked to ASD [7, 45]. By analyzing extensive genomic and proteomic datasets, these technologies have identified genetic variations and enzyme deficiencies, particularly in Dipeptidyl Peptidase-IV (DPP-IV), an essential enzyme for breaking down dietary proteins like gluten and casein, commonly found in wheat and dairy products. DPP-IV facilitates protein digestion by removing dipeptides from the N-terminus of polypeptides, which is crucial for their breakdown and absorption. If DPP-IV activity is lacking or blocked, it may cause incomplete breakdown of gluten and casein, leading to the creation and buildup of peptide fragments with potential neuroactive effects. Similarly, Tissue Transglutaminase (tTG), an enzyme that alters gluten peptides, can enhance their immunogenicity and initiate an autoimmune reaction in genetically susceptible individuals [46, 47], thereby hindering the digestion of gluten and casein.

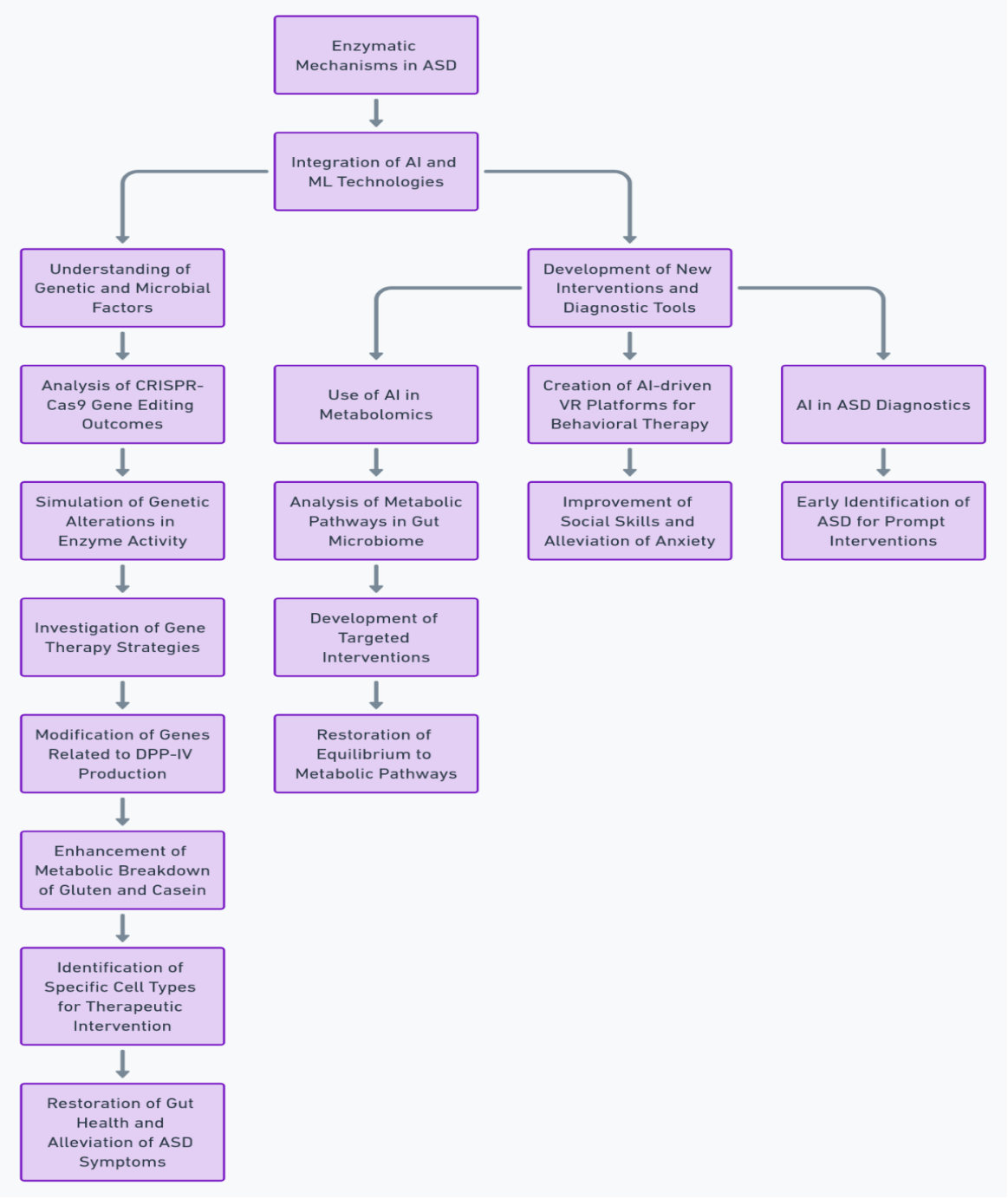

Figure 3 The diagram demonstrates the incorporation of artificial intelligence and machine learning in studying enzymatic dysfunctions in ASD, emphasizing progress in genetic analysis, therapeutic interventions, and diagnostic tools development.

A comprehensive understanding of these mechanisms allows for accurate predictions of individual susceptibilities to dietary proteins and enables the customization of dietary interventions that could potentially alleviate symptoms associated with ASD. CRISPR-Cas9 gene editing holds promise for the future of ASD treatment by addressing the underlying genetic causes of enzymatic dysfunctions [48]. Through the modification of genes associated with enzyme production, CRISPR-Cas9 presents a promising opportunity to address metabolic pathways impacted by ASD, potentially alleviating the dietary effects on the disorder's symptoms.

The utilization of scRNA-seq technology has yielded significant findings regarding the cellular diversity within the gut of individuals with ASD [49]. Understanding this level of detail is essential for developing targeted therapies aimed at restoring normal gut function and potentially alleviating ASD symptoms. Additionally, studies on metabolomics and the microbiome have successfully charted the distinct metabolic and microbial characteristics of individuals with ASD [50, 51]. These findings demonstrate the connection between variations in gut microbiota and metabolic profiles and the manifestation of dietary sensitivities and symptoms, as shown in Figure 4.

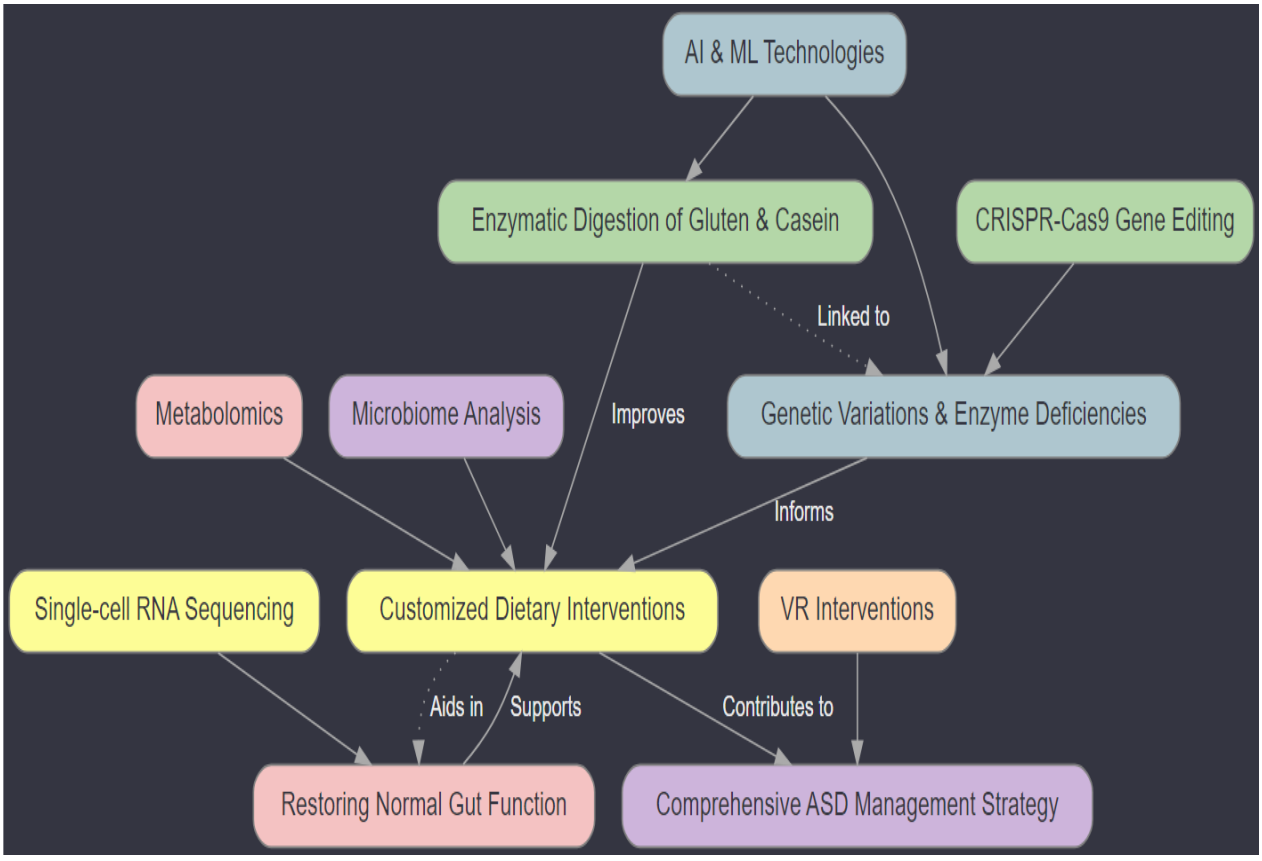

Figure 4 Elucidating the Mechanisms of Gluten and Casein Digestion in ASD Through the Integration of Artificial Intelligence, Genomic Technologies, and Virtual Reality Interventions

Furthermore, VR technologies have been employed to develop immersive social and cognitive training programs tailored to individuals with ASD [52, 53]. These programs are personalized using AI to address the specific requirements of each user. While these interventions significantly impact a comprehensive ASD management strategy by improving quality of life and functional outcomes, they are not directly related to dietary protein metabolism.

The Gut-Brain Axis: Enzymatic and Microbial Interactions

Researchers are currently investigating the use of CRISPR-Cas9 gene editing to target specific gene modifications, such as those related to zonulin [54], a protein responsible for regulating gut permeability. These studies aim to address gut barrier integrity issues [55, 56] that could be associated with ASD. ScRNA-seq has revealed the presence of overactive microglia in the brain and distinct epithelial and immune cell subsets in the gut, suggesting their potential significance in the pathophysiology of ASD [57, 58].

Metabolomics approaches have uncovered distinct metabolic byproducts, such as modified profiles of short-chain fatty acids (SCFAs), which can serve as potential biomarkers for gut dysbiosis or malabsorption in individuals with ASD [59, 60]. Microbiome analyses have identified imbalances in certain bacterial strains, including a decrease in *Faecalibacterium prausnitzii* and an increase in *Clostridium difficile* [61, 62]. These findings provide specific targets for probiotic interventions. AI and ML have effectively analyzed these data streams, identifying genetic polymorphisms and enzyme deficiencies, such as those found in the DPP-IV enzyme, that are associated with ASD symptoms [63, 64].

Nutritional Considerations and Enzymatic Interventions

The management of nutrition in Autism Spectrum Disorder (ASD) extends beyond conventional methods by incorporating advanced technologies such as CRISPR-Cas9 gene editing, scRNA-seq, metabolomics, microbiome analysis, and AI and ML algorithms. These technologies significantly improve the customization of dietary and enzyme supplementation strategies, enabling a precision medicine approach to alleviate symptoms associated with ASD.

CRISPR-Cas9 gene editing shows promise in addressing genetic variations that impact the efficiency of enzymes involved in breaking down dietary proteins like gluten and casein [65]. These proteins are frequently linked to the exacerbation of ASD symptoms. This approach has the potential to address dietary sensitivities at their genetic root by precisely modifying genes associated with enzyme production.

ScRNA-seq technology provides valuable insights into the cellular landscape of the gut and its interaction with dietary components [66]. By identifying distinct cell types and states that play a role in the enzymatic environment of the gut and its effects on gut health, scRNA-seq offers crucial insights into how individual cell mechanisms impact the efficacy of dietary changes and enzyme supplementation in individuals with ASD [67].

Metabolomics and microbiome analysis enhance our understanding of the biochemical and microbial context in which dietary interventions function [68, 69]. Metabolomics can detect distinct metabolic signatures that reveal how individuals with ASD metabolize different types of food [70, 71]. This information is valuable for tailoring personalized diet plans. Microbiome analysis provides insights into the gut bacterial profiles associated with ASD [72, 73], which can guide the selection of probiotics or dietary adjustments aimed at restoring a healthy balance of gut flora.

AI and ML are at the forefront of integrating diverse data streams to predict individual responses to dietary interventions [74, 75]. By comprehensively analyzing genetic, cellular, metabolic, and microbial information, these technologies facilitate the creation of personalized nutrition strategies.

Challenges and limitations of research

Studying enzyme functions and utilizing AI in ASD treatment present numerous challenges and constraints, along with ethical considerations crucial for directing these scientific pursuits conscientiously. Enzyme activity variability across the ASD population poses a significant research challenge, making it difficult to establish standardized treatment protocols. This variability affects both the metabolic breakdown of dietary components and the effectiveness of enzyme supplementation, necessitating personalized intervention strategies. Additionally, the diverse range of dietary responses underscores the complexity of customizing dietary adjustments, requiring a thorough understanding of each patient's specific enzymatic profile and dietary sensitivities [76].

The integration of AI and ML in ASD research adds another layer of complexity. While these technologies have the potential to transform the diagnosis and treatment of ASD and its GI comorbidities, they also raise ethical concerns regarding data privacy [77], informed consent [78], and algorithmic bias [79]. It is essential to prioritize the confidentiality and security of sensitive health information by adhering to data protection regulations and ethical standards. Informed consent procedures should clearly communicate the use of AI in both research and clinical environments, outlining the associated risks and benefits. Furthermore, algorithmic bias poses a significant ethical dilemma [80-82], necessitating careful attention to ensure AI models are trained on diverse datasets to avoid perpetuating inequalities in diagnosis and treatment.

The implementation of AI-driven insights and genetic editing technologies such as CRISPR-Cas9 in clinical settings also encounters challenges related to effectiveness, safety, and the ethical implications of gene editing [83-85]. Thorough safety assessments and ethical discussions are crucial regarding genetic modifications in therapeutic applications due to the possibility of unintended consequences.

Future Directions in Autism Spectrum Disorder research

The future of ASD research is shifting towards a precision medicine paradigm that incorporates AI, ML, and genetic editing technologies. Future research is likely to utilize multi-omic data integration, incorporating genomic, proteomic, metabolomic, and microbiome data to understand the intricate causes of ASD and its GI issues. The primary emphasis will be on enhancing AI and ML algorithms to accurately predict individual responses to dietary and enzyme supplementation strategies, facilitating personalized treatment plans. Advancements in CRISPR-Cas9 gene editing will focus on exploring corrective interventions for enzyme deficiencies, with attention to safety, efficacy, and ethical considerations. Microbiome engineering will become a crucial therapeutic approach, aimed at improving gut health by precisely adjusting gut flora based on AI-driven assessments. Single-cell technologies will enhance our understanding of the cellular basis of ASD, providing new therapeutic targets and in-depth mechanistic insights. Amidst these advancements, establishing robust ethical and regulatory frameworks will be essential to address privacy, consent, and equity issues, ensuring the ethical use of these innovative technologies. Overall, the combination of these new methods will likely mark a new phase in ASD research and treatment, characterized by a focus on tailored, precise interventions.

CONCLUSION

The combination of AI, ML, CRISPR-Cas9 gene editing, and single-cell RNA sequencing represents significant progress in the understanding and management of ASD and its GI comorbidities. This article highlights the critical role of these technologies in elucidating the intricate relationship between the gut and the brain, revealing genetic, enzymatic, and microbial factors associated with ASD. AI and ML have been instrumental in customizing interventions through the analysis of extensive datasets, allowing for the identification

of enzyme deficiencies and microbial imbalances linked to GI symptoms in individuals with ASD. CRISPR-Cas9 holds promise for developing targeted therapies by directly addressing enzyme deficiencies. Additionally, single-cell RNA sequencing has unveiled cellular heterogeneity in the ASD gut, offering new avenues for therapeutic strategies. The variability in enzyme activity and dietary responses among individuals with ASD underscores the need for a highly individualized treatment approach, while also raising important ethical issues related to data privacy, informed consent, and algorithmic bias. Future research should focus on leveraging these technologies, with an emphasis on integrating multi-omic data to better understand the complexities of ASD and its GI comorbidities. The potential for precision medicine in ASD is promising, offering the opportunity to enhance the quality of life for affected individuals and their families by overcoming existing barriers and addressing ethical concerns. Advanced technologies in ASD research illuminate complex biological processes and enable personalized interventions.

REFERENCES

1 Casanova M.F., Frye R.E., Gillberg C., Casanova E.L. Comorbidity and autism spectrum disorder. *Frontiers in psychiatry*. 2020; 11: 1273.

2 Leader G., O'Reilly M., Gilroy S.P., Chen J.L., Ferrari C., Mannion A. Comorbid feeding and gastrointestinal symptoms, challenging behavior, sensory issues, adaptive functioning and quality of life in children and adolescents with autism spectrum disorder. *Dev Neurorehabil*. 2021; 24(1): 35-44.

3 Alkhatib A., Nusseir K., Abdo N., Alshare Q., Altawalbeh O. Behavioral Interventions with and without Pharmacological Treatment: A Comparative Study at An Autistic Center in Jordan. *Jordan Journal of Pharmaceutical Sciences*. 2024; 17(2): 395-406.

4 Mesleh A.G., Abdulla S.A., El-Agnaf O. Paving the way toward personalized medicine: current advances and challenges in multi-OMICS approach in autism spectrum disorder for biomarkers discovery and patient stratification. *Journal of personalized medicine*. 2021; 11(1): 41.

5 Lim E.T., Chan Y., Dawes P., Guo X., Erdin S., Tai D.J., et al. Orgo-Seq integrates single-cell and bulk transcriptomic data to identify cell type specific-driver genes associated with autism spectrum disorder. *Nature Communications*. 2022; 13(1): 3243.

6 Higdon R., Earl R.K., Stanberry L., Hudac C.M., Montague E., Stewart E., et al. The promise of multi-omics and clinical data integration to identify and target personalized healthcare approaches in autism spectrum disorders. *Omics: a journal of integrative biology*. 2015; 19(4): 197-208.

7 Ristori M.V., Mortera S.L., Marzano V., Guerrera S., Vernocchi P., Ianiro G., et al. Proteomics and metabolomics approaches towards a functional insight onto AUTISM spectrum disorders: phenotype stratification and biomarker discovery. *Int J Mol Sci*. 2020; 21(17): 6274.

8 Qureshi F. Seize the Data: Addressing Research Challenges Among Children with Autism Spectrum Disorder Using Statistical and Machine Learning Techniques. *Rensselaer Polytechnic Institute*; 2022.

9 Ferina J., Kruger M., Kruger U., Ryan D., Anderson C., Foster J., et al. Predicting Problematic Behavior in Autism Spectrum Disorder Using Medical History and Environmental Data. *Journal of Personalized Medicine*. 2023; 13(10): 1513.

10 Mann M., Kumar C., Zeng W-F., Strauss M.T. Artificial intelligence for proteomics and biomarker discovery. *Cell systems*. 2021; 12(8): 759-770.

11 Azencott C-A. Machine learning tools for biomarker discovery. Sorbonne Université, UPMC; 2020.

12 Agha A.S.A., Khalil E., Al-Remawi M., Al-Akayleh F. Infrared Microscopy: A Multidisciplinary Review of Techniques, Applications, and Ethical Dimensions. *Jordan Journal of Pharmaceutical Sciences*. 2024; 17(2): 267-291.

13 Al-Biltagi M., Saeed N.K., Qaraghuli S. Gastrointestinal disorders in children with autism: Could artificial intelligence help? *Artificial Intelligence in Gastroenterology*. 2022; 3(1): 1-12.

14 Randolph-Gips M., & Srinivasan P. Modeling autism: a systems biology approach. *J Clin Bioinforma*. 2012; 2(1): 1-15.

15 Al-Beltagi M., Saeed N.K., Bediwy A.S., Elbeltagi R., Alhawamdeh R. Role of gastrointestinal health in managing children with autism spectrum disorder. *World Journal of Clinical Pediatrics*. 2023; 12(4): 171.

16 Peralta-Marzal L.N., Rojas-Velazquez D., Rigters D., Prince N., Garssen J., Kraneveld A.D., et al. A robust microbiome signature for autism spectrum disorder across different studies using machine learning. *Sci Rep*. 2024; 14(1): 814.

17 Frye R.E. A personalized multidisciplinary approach to evaluating and treating autism spectrum disorder. *Journal of Personalized Medicine*. 2022; 12(3): 464.

18 Larroya A., Pantoja J., Codoñer-Franch P., Cenit M.C. Towards tailored gut microbiome-based and dietary interventions for promoting the development and maintenance of a healthy brain. *Frontiers in Pediatrics*. 2021; 9: 705859.

19 Mandecka A., & Regulska-Ilow B. The importance of nutritional management and education in the treatment of autism. *Rocz Panstw Zakl Hig*. 2022; 73(3).

20 Cui C., Yang H., Wang Y., Zhao S., Asad Z., Coburn L.A., et al. Deep multi-modal fusion of image and non-image data in disease diagnosis and prognosis: a review. *Progress in Biomedical Engineering*. 2023.

21 Singh M.P., Agrawal N.R., Saurabh S., Krishna E., Singh J.M., Agrawal N. Exploring Therapeutic Digestive Enzyme Landscape in India: Current Evidence, Profit Motives, Regulations, and Future Perspectives. *Cureus*. 2024; 16(1).

22 Yenkoyan K., Ounanian Z., Mirumyan M., Hayrapetyan L., Zakaryan N., Sahakyan R., et al. Advances in the Treatment of Autism Spectrum Disorder: Current and Promising Strategies. *Curr Med Chem*. 2024; 31(12): 1485-1511.

23 James D.M., Davidson E.A., Yanes J., Moshiree B., Dallman J.E. The gut-brain-microbiome axis and its link to autism: emerging insights and the potential of zebrafish models. *Frontiers in cell and developmental biology*. 2021; 9: 662916.

24 Gonatopoulos-Pournatzis T., Wu M., Braunschweig U., Roth J., Han H., Best A.J., et al. Genome-wide CRISPR-Cas9 interrogation of splicing networks reveals a mechanism for recognition of autism-misregulated neuronal microexons. *Mol Cell*. 2018; 72(3): 510-524. e512.

25 Walker S.J., Langefeld C.D., Zimmerman K., Schwartz M.Z., Krigsman A. A molecular biomarker for prediction of clinical outcome in children with ASD, constipation, and intestinal inflammation. *Sci Rep*. 2019; 9(1): 5987.

26 Lin C-W, Septyaningtrias D.E., Chao H-W, Konda M., Atarashi K., Takeshita K., et al. A common epigenetic mechanism across different cellular origins underlies systemic immune dysregulation in an idiopathic autism mouse model. *Mol Psychiatry*. 2022; 27(8): 3343-3354.

27 Goel K., Goel K., Bansal S., Gupta S. Coding to Cure: AI Revolutionizing Precision Medicines for Genetic Disorders. Available at SSRN 4594339 2023.

28 Gupta D., Bhattacharjee O., Mandal D., Sen M.K., Dey D., Dasgupta A., et al. CRISPR-Cas9 system: A new-fangled dawn in gene editing. *Life Sci*. 2019; 232: 116636.

29 Kim H.K., Yu G., Park J., Min S., Lee S., Yoon S., et al. Predicting the efficiency of prime editing guide RNAs in human cells. *Nat Biotechnol*. 2021; 39(2): 198-206.

30 Zhou L., & Yao S. Recent advances in therapeutic CRISPR-Cas9 genome editing: mechanisms and applications. *Molecular Biomedicine*. 2023; 4(1): 10.

31 Sandhu A., Kumar A., Rawat K., Gautam V., Sharma A., Saha L. Modernising autism spectrum disorder model engineering and treatment via CRISPR-Cas9: A gene reprogramming approach. *World Journal of Clinical Cases*. 2023; 11(14): 3114.

32 Jovic D., Liang X., Zeng H., Lin L., Xu F., Luo Y. Single-cell RNA sequencing technologies and applications: A brief overview. *Clinical and Translational Medicine*. 2022; 12(3): e694.

33 Tan H., Wang W., Zhou C., Wang Y., Zhang S., Yang P., et al. Single-cell RNA-seq uncovers dynamic processes orchestrated by RNA-binding protein DDX43 in chromatin remodeling during spermiogenesis. *Nature Communications*. 2023; 14(1): 2499.

34 Griffin A., Chen M., Tiwari V.K. Dissection of cellular disruptions in autism spectrum disorder comorbidities. *Eur J Neurosci*. 2023; 58(9): 3921-3931.

35 Olivares M., Schüppel V., Hassan A.M., Beaumont M., Neyrinck A.M., Bindels L. B., et al. The potential role of the dipeptidyl peptidase-4-like activity from the gut microbiota on the host health. Front Microbiol 2018; 9: 1900.

36 Singh S., Sarma D.K., Verma V., Nagpal R., Kumar M. Unveiling the future of metabolic medicine: omics technologies driving personalized solutions for precision treatment of metabolic disorders. *Biochemical and Biophysical Research Communications*. 2023.

37 Liu J., Gao Z., Liu C., Liu T., Gao J., Cai Y., et al. Alteration of gut microbiota: new strategy for treating autism spectrum disorder. Frontiers in Cell and Developmental Biology 2022; 10: 792490.

38 Kaur H., Singh Y., Singh S., Singh R.B. Gut microbiome-mediated epigenetic regulation of brain disorder and application of machine learning for multi-omics data analysis. Genome 2021; 64(4): 355-371.

39 Karami B., Koushki R., Arabgol F., Rahmani M., Vahabie A-H. Effectiveness of virtual/augmented reality–based therapeutic interventions on individuals with autism spectrum disorder: a comprehensive meta-analysis. *Frontiers in Psychiatry*. 2021; 12: 665326.

40 Zhang M., Ding H., Naumceska M., Zhang Y. Virtual reality technology as an educational and intervention tool for children with autism spectrum disorder: current perspectives and future directions. *Behavioral Sciences*. 2022; 12 (5): 138.

41 Ferrari E. Artificial Intelligence for Autism Spectrum Disorders. *Artificial Intelligence in Medicine: Springer*. 2021; 1-15.

42 Baribeau D., Anagnostou E. Novel treatments for autism spectrum disorder based on genomics and systems biology. *Pharmacol Ther*. 2022; 230: 107939.

43 Karhu E., Zukerman R., Eshraghi R.S., Mittal J., Deth R.C., Castejon A.M., et al. Nutritional interventions for autism spectrum disorder. *Nutr Rev*. 2020; 78(7): 515-531.

44 Tayanloo-Beik A., Hamidpour S.K., Abedi M., Shojaei H., Tavirani M.R., Namazi N., et al. Zebrafish modeling of autism spectrum disorders, current status and future prospective. *Frontiers in Psychiatry*. 2022; 13: 911770.

45 Gupta C., Chandrashekar P., Jin T., He C., Khullar S., Chang Q., et al. Bringing machine learning to research on intellectual and developmental disabilities: Taking inspiration from neurological diseases. *J Neurodev Disord*. 2022; 14(1): 28.

46 Zou H. iDPPIV-SI: identifying dipeptidyl peptidase IV inhibitory peptides by using multiple sequence information. *Journal of Biomolecular Structure and Dynamics*. 2023: 1-9.

47 Carvalho E.A., Santana C.P., Rodrigues I.D., Lacerda L., Bastos G.S. Hidden Markov models to estimate the probability of having autistic children. *IEEE Access*. 2020; 8: 99540-99551.

48 Forgham H., Liu L., Zhu J., Javed I., Cai W., Qiao R., et al. Vector enabled CRISPR gene editing–A revolutionary strategy for targeting the diversity of brain pathologies. *Coord Chem Rev*. 2023; 487: 215172.

49 Ghosh A., Nadella N., Monaghan-Nichols A.P., Chu X-P. Gene therapy as an emerging treatment for Scn2a mutation-induced autism spectrum disorders. *Fundamental Research*. 2023.

50 Graham S.F., Turkoglu O., Yilmaz A., Ustun I., Ugur Z., Bjorndhal T., et al. Targeted metabolomics highlights perturbed metabolism in the brain of autism spectrum disorder sufferers. *Metabolomics*. 2020; 16: 1-15.

51 Sotelo-Orozco J., Schmidt R.J., Slupsky C.M., Hertz-Picciotto I. Investigating the Urinary Metabolome in the First Year of Life and Its Association with Later Diagnosis of Autism Spectrum Disorder or Non-Typical Neurodevelopment in the MARBLES Study. *Int J Mol Sci*. 2023; 24(11): 9454.

52 Parsons S., & Mitchell P. The potential of virtual reality in social skills training for people with autistic spectrum disorders. *Journal of intellectual disability research*. 2002; 46(5): 430-443.

53 Herrero J.F., & Lorenzo G. An immersive virtual reality educational intervention on people with autism spectrum disorders (ASD) for the development of communication skills and problem solving. *Education and Information Technologies*. 2020; 25: 1689-1722.

54 Goh Y.J., & Barrangou R. Harnessing CRISPR-Cas systems for precision engineering of designer probiotic lactobacilli. *Curr Opin Biotechnol*. 2019; 56: 163-171.

55 Rossi M. Biotechnological Strategies for the Treatment of Gluten Intolerance: Academic Press. 2021.

56 Moysidou C-M. A 3D in Vitro Model of the Human Gut-microbiome: A Bioelectronics Approach. University of Cambridge; 2020.

57 Afridi R., Seol S., Kang H.J., Suk K. Brain-immune interactions in neuropsychiatric disorders: Lessons from transcriptome studies for molecular targeting. *Biochem Pharmacol*. 2021; 188: 114532.

58 Zamora-Moratalla A., de Lagrán M.M., Dierssen M. Neurodevelopmental disorders: 2021 update. *Free Neuropathology*. 2021; 2.

59 Wang L., Conlon M.A., Christophersen C.T., Sorich M.J., Angley M.T. Gastrointestinal microbiota and metabolite biomarkers in children with autism spectrum disorders. *Biomark Med*. 2014; 8(3): 331-344.

60 Srikantha P., & Mohajeri M.H. The possible role of the microbiota-gut-brain-axis in autism spectrum disorder. *Int J Mol Sci*. 2019; 20(9): 2115.

61 De Angelis M., Piccolo M., Vannini L., Siragusa S., De Giacomo A., Serrazzanetti D.I., et al. Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. *PLoS One*. 2013; 8(10): e76993.

62 Oh D., Cheon K-A. Alteration of gut microbiota in autism spectrum disorder: An overview. *Journal of the Korean Academy of Child and Adolescent Psychiatry*. 2020; 31(3): 131.

63 Roesner L., Traidl S., Kienlin P., Begemann G., Jing L., Koelle D., et al. Symposium on Atopic Dermatitis, 11–13 April 2018, Utrecht, the Netherlands. *Symposium on Atopic Dermatitis.* 11. 2018:13.

64 Ruggeri B., Sarkans U., Schumann G., Persico A.M. Biomarkers in autism spectrum disorder: the old and the new. *Psychopharmacology*. 2014; 231: 1201-1216.

65 Naeem M., Manzoor S., Abid M-U-H, Tareen M.B.K., Asad M., Mushtaq S., et al. Fungal proteases as emerging biocatalysts to meet the current challenges and recent developments in biomedical therapies: An updated review. *Journal of Fungi*. 2022; 8(2): 109.

66 Wang X., Cheng X., Liu H., Mu X., Zheng H. Food nutrition and toxicology targeting on specific organs in the era ofsingle-cell sequencing. *Food Science and Human Wellness*. 2024; 13(1): 75-89.

67 Hoffmann A., & Spengler D. Single-cell transcriptomics supports a role of CHD8 in autism. *Int J Mol Sci*. 2021; 22(6): 3261.

68 Moco S., Ross A.B. Can we use metabolomics to understand changes to gut microbiota populations and function? A nutritional perspective. *Metabonomics and gut microbiota in nutrition and disease*. 2015: 83-108.

69 Shaffer M., Armstrong A.J., Phelan V.V., Reisdorph N., Lozupone C.A. Microbiome and metabolome data integration provides insight into health and disease. *Translational Research*. 2017; 189: 51-64.

70 Orozco J.S., Hertz-Picciotto I., Abbeduto L., Slupsky C.M. Metabolomics analysis of children with autism, idiopathic-developmental delays, and Down syndrome. *Translational Psychiatry*. 2019; 9(1): 243. 10.1038/s41398-019-0578-3

71 Bahti A., Telfah A., Sharar N., Jafar H., Hergenröder R. Nuclear Magnetic Resonance for Targeted Metabolomics and Biochemical Sensor. *Jordan Journal of Pharmaceutical Sciences*. 2023; 16(2): 469-469.

72 Dan Z., Mao X., Liu Q., Guo M., Zhuang Y., Liu Z., et al. Altered gut microbial profile is associated with abnormal metabolism activity of Autism Spectrum Disorder. *Gut microbes*. 2020; 11(5): 1246-1267.

73 Morton J.T., Jin D-M, Mills R.H., Shao Y., Rahman G., McDonald D., et al. Multi-level analysis of the gut–brain axis shows autism spectrum disorder-associated molecular and microbial profiles. *Nat Neurosci*. 2023: 1-10.

74 Oyebode O., Fowles J., Steeves D., Orji R. Machine learning techniques in adaptive and personalized systems for health and wellness. *International Journal of Human–Computer Interaction*. 2023; 39(9): 1938-1962.

75 Sahu M., Gupta R., Ambasta R.K., Kumar P. Artificial intelligence and machine learning in precision medicine: A paradigm shift in big data analysis. P*rog Mol Biol Transl Sci*. 2022; 190(1): 57-100.

76 O'sullivan A., Henrick B., Dixon B., Barile D., Zivkovic A., Smilowitz J., et al. 21st century toolkit for optimizing population health through precision nutrition. *Critical reviews in food science and nutrition*. 2018; 58(17): 3004-3015.

77 Stahl B.C., & Wright D. Ethics and privacy in AI and big data: Implementing responsible research and innovation. *IEEE Security & Privacy*. 2018; 16(3): 26-33.

78 Cohen I.G. Informed consent and medical artificial intelligence: What to tell the patient? *Geo LJ*. 2019; 108: 1425.

79 Ntoutsi E., Fafalios P., Gadiraju U., Iosifidis V., Nejdl W., Vidal M.E., et al. Bias in data-driven artificial intelligence systems—An introductory survey. *Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery*. 2020; 10(3): e1356.

80 Kordzadeh N., & Ghasemaghaei M. Algorithmic bias: review, synthesis, and future research directions. *European Journal of Information Systems*. 2022; 31(3): 388-409.

81 Al-Akayleh F., Agha A.S.A. Trust, Ethics, and User-Centric Design in AI-Integrated Genomics. *2024 2nd International Conference on Cyber Resilience (ICCR).* IEEE; 2024:1-6.

82 Al-Akayleh F., Ali Agha A.S.A., Abdel Rahem R.A., Al-Remawi M. A mini review on the applications of artificial intelligence (AI) in surface chemistry and catalysis. 2024; 61(4): 285-296. doi:10.1515/tsd-2024-2580

83 Rasul M.F., Hussen B.M., Salihi A., Ismael B.S., Jalal P.J., Zanichelli A., et al. Strategies to overcome the main challenges of the use of CRISPR/Cas9 as a replacement for cancer therapy. *Mol Cancer*. 2022; 21(1): 64.

84 Al-Akayleh F., Al-Remawi M., Agha A.S.A. AI-Driven Physical Rehabilitation Strategies in Post-Cancer Care. *2024 2nd International Conference on Cyber Resilience (ICCR).* IEEE; 2024:1-6.

85 Aburub F., & Agha A.S.A. AI-Driven Psychological Support and Cognitive Rehabilitation Strategies in Post-Cancer Care. *2024 2nd International Conference on Cyber Resilience (ICCR).* IEEE; 2024:1-6.

دمج الذكاء الاصطناعي والتقنيات الجينومية المتقدمة في استكشاف اضطراب طيف التوحد والمشكلات المعدية المعوية المصاحبة: نهج متعدد نحو التشخيص الدقيق

لمى غنيم[1] ، أحمد سعد عبدالباري علي اغا[2]، طلال ابورجيع[2]*

[1] قسم الارشاد و التربية الخاصة، كلية العلوم التربوية، الجامعة الأردنية، عمان، الأردن

[2] قسم العلوم الصيدلانية، كلية الصيدلة، الجامعة الأردنية، عمان، الأردن.

ملخص

هذا المقال يسلط الضوء على التأثير المحتمل للذكاء الاصطناعي والتعلم الآلي وتقنية تحرير الجينات كريسبر–كاس9 وتسلسل الحمض النووي الريبوزي للخلايا الفردية على تحسين الفهم والإدارة لاضطراب طيف التوحد ومشكلات الجهاز الهضمي المصاحبة له. يتناول هذا البحث الية كشف هذه التقنيات للعلاقة المعقدة بين الأمعاء والدماغ، مشيرًا إلى نقص في إنزيمات محددة وخلل في التوازن الميكروبي مرتبط بأعراض الجهاز الهضمي في اضطراب طيف التوحد حيث انه من خلال استخدام الذكاء الاصطناعي والتعلم الآلي، يتم تطوير استراتيجيات تدخّل مُصممة خصيصًا عبر تحليل البيانات الجينومية والبروتيومية والبيئية، مما يعزز قدرتنا على التنبؤ بمشاكل الجهاز الهضمي في اضطراب طيف التوحد ومعالجتها. بالإضافة إلى ذلك، تعد تقنية تحرير الجينات كريسبر–كاس9 طريقة مبشرة لتصحيح العيوب الجينية المرتبطة بإنتاج الإنزيمات، ما يتيح الحصول على علاجات محددة. يوفر تسلسل الحمض النووي الريبوزي للخلايا الفردية رؤى قيمة حول تنوع الخلايا في أمعاء مرضى اضطراب طيف التوحد، كاشفاً عن اتجاهات علاجية جديدة. يبرز هذا البحث إلامكانات الواعدة لهذه التقنيات واهميتها مع الإشارة أيضًا إلى التحديات والمسائل الأخلاقية المتعلقة باستخدامها، مؤكدًا على أهمية النهج المتعدد التخصصات للاستفادة الكاملة من مزاياها لعلاج مرضى التوحد.

الكلمات الدالة: اضطرابات طيف التوحد؛ الخلل الوظيفي الإنزيمي؛ التدخلات الغذائية؛ الاضطرابات المعوية المرتبطة؛ العلاج الغذائي المُفَصَّل.

* ***المؤلف المراسل: طلال ابورجيع***

aburjai@ju.edu.jo

تاريخ استلام البحث 2024/02/19 وتاريخ قبوله للنشر 2024/04/04.