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Nanomedicine & Nanotechnology Open Access
ISSN: 2574-187X

Artificial Intelligence Enabled Intelligent Nanoparticle for Precision Therapeutics in Persistent Post-Covid Syndrome: A Next Generation Translational Medicine Perspective

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Research Article

Volume 11 Issue 3

Received Date: August 21, 2026

Published Date: September 10, 2026

DOI: 10.23880/nnoa-16000357

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Abstract

Persistent Post-COVID Syndrome (PPCS), commonly known as Long COVID, has emerged as a major global health challenge affecting millions of individuals after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Its heterogeneous clinical manifestations, prolonged symptom duration, and complex pathophysiological mechanisms including chronic inflammation, immune dysregulation, endothelial dysfunction, mitochondrial impairment, viral persistence, and microvascular injury continue to hinder accurate diagnosis and effective treatment. Recent advances in artificial intelligence (AI) and nanotechnology offer promising opportunities to improve PPCS management through precision medicine. AI-driven computational platforms facilitate rapid analysis of multidimensional clinical, imaging, and genomic, proteomic, metabolomics, and immunological data, enabling early diagnosis, disease stratification, biomarker identification, and prediction of therapeutic outcomes. Concurrently, intelligent nanoparticle engineering enhances targeted drug delivery, controlled therapeutic release, immune modulation, improved bioavailability, and real-time bio sensing, overcoming several limitations of conventional therapies. The integration of AI with intelligent nanoparticle systems has established a novel translational medicine approach for personalized healthcare. AI-assisted nanoparticle design optimizes material properties, predicts toxicity and pharmacokinetics, and supports individualized therapeutic strategies with improved efficacy and safety. This review highlights the role of AI-enabled intelligent nanoparticles in precision therapeutics for PPCS, emphasizing recent advances in precision diagnostics, targeted drug delivery, immune modulation, biosensor-based monitoring, and future translational applications. The convergence of AI and Nano medicine has the potential to transform the diagnosis, treatment, and long-term management of Persistent Post-COVID Syndrome.

Keywords: Artificial Intelligence; Persistent Post-COVID Syndrome; Nanotechnology; Intelligent Nanoparticles and Precision Medicine

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has had a profound impact on global health, leaving many individuals with persistent symptoms even after recovery from acute infection [1]. This condition, known as Persistent Post-COVID Syndrome (PPCS) or Long COVID, is characterized by prolonged fatigue, cognitive dysfunction, dyspnoea, musculoskeletal pain, cardiovascular abnormalities, and reduced quality of life. The heterogeneous clinical presentation and complex pathophysiology, involving chronic inflammation, immune dysregulation, endothelial dysfunction, mitochondrial impairment, oxidative stress, and viral persistence, make diagnosis and treatment particularly challenging. Recent advances in artificial intelligence (AI) and nanotechnology have introduced innovative strategies for precision medicine in PPCS. AI enables rapid analysis of multidimensional clinical, imaging, and genomic, proteomic, and immunological data, facilitating early diagnosis, disease stratification, biomarker discovery, and prediction of therapeutic outcomes.

Meanwhile, intelligent nanoparticles provide targeted drug delivery, controlled therapeutic release, immune modulation, and enhanced bioavailability, thereby improving treatment efficacy while minimizing systemic toxicity. The integration of AI with intelligent nanoparticle engineering has established a next-generation translational medicine platform for personalized healthcare. AI-guided nanoparticle design optimizes therapeutic performance, predicts safety profiles, and supports individualized treatment planning. Furthermore, biosensors, wearable technologies, digital twins, and multi-omics approaches enable continuous patient monitoring and precision therapeutic interventions [2]. This review highlights recent advances in AI-enabled intelligent nanoparticles for precision therapeutics in Persistent Post-COVID Syndrome and discusses their clinical applications, translational potential, current challenges, and future perspectives in advancing personalized medicine.

Pathophysiological Basis of PPCS

Persistent Post-COVID Syndrome (PPCS) is a complex multisystem disorder characterized by prolonged physiological disturbances that persist beyond recovery from acute SARS-CoV-2 infection. Its pathogenesis involves persistent immune dysregulation, chronic inflammation, endothelial dysfunction, mitochondrial impairment, oxidative stress, autonomic imbalance, and metabolic alterations [3]. Elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), contribute to sustained immune activation, chronic tissue inflammation, and multisystem dysfunction. Endothelial injury impairs microvascular circulation and oxygen delivery, resulting in fatigue, dyspnoea, cardiovascular complications, and neurological manifestations. Mitochondrial dysfunction reduces cellular ATP production and increases reactive oxygen species (ROS), leading to chronic fatigue, muscle weakness, and cognitive impairment. Persistent viral antigens and autoimmune responses may further maintain chronic immune activation and disease progression in Table 1 and Figure 1. The biological heterogeneity of PPCS highlights the need for precision diagnostic approaches capable of identifying patient-specific molecular abnormalities and guiding personalized therapeutic interventions.

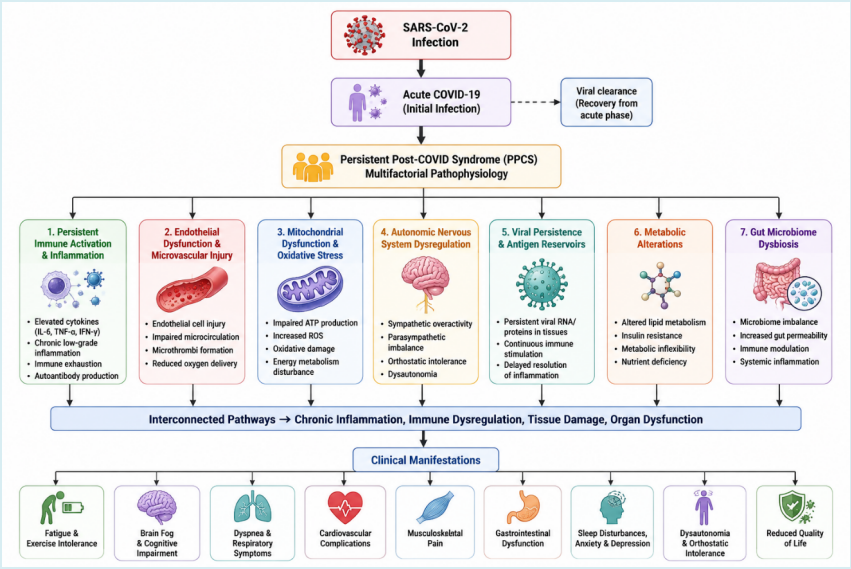


Figure 1: Pathophysiological basis of PPCS.

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Pathophysiological Mechanism	Clinical Manifestations	AI Application	Nanoparticle-Based Strategy
Chronic inflammation	Fatigue, myalgia	Cytokine prediction	Anti-inflammatory nanoparticle delivery
Immune dysregulation	Autoimmune manifestations	Immune profiling	Immunomodulatory nanoparticles
Endothelial dysfunction	Microvascular injury	Risk prediction models	Endothelial-targeted Nano carriers
Oxidative stress	Cellular damage	Biomarker analysis	Antioxidant nanoparticles
Mitochondrial dysfunction	Chronic fatigue	Metabolic modelling	Mitochondria-targeted nanoparticles
Viral persistence	Persistent symptoms	Viral antigen detection	Antiviral Nano therapeutics

Table 1: Pathophysiological Mechanisms of Persistent Post-COVID Syndrome and Potential AI–Nanoparticle Intervention.

Current Diagnostic Challenges in PPCS

The diagnosis of Persistent Post-COVID Syndrome (PPCS) remains primarily clinical because there are currently no universally accepted diagnostic biomarkers. Patients often present with nonspecific symptoms such as fatigue, cognitive impairment, dyspnoea, and musculoskeletal pain, which overlap with chronic fatigue syndrome, fibromyalgia, autoimmune disorders, and other post-viral illnesses. Routine laboratory investigations and conventional imaging frequently appear normal despite significant functional impairment, making early diagnosis difficult [4]. The heterogeneous nature of PPCS, influenced by age, sex, genetic factors, immune responses, vaccination status, and pre-existing comorbidities, further complicates clinical assessment and treatment. Major diagnostic limitations include the lack of standardized biomarkers, variable symptom progression, limited integration of clinical and multi-omics data, delayed recognition due to symptom overlap, and inadequate predictive tools for disease progression and therapeutic response. These challenges emphasize the need for artificial intelligence-based computational approaches that integrate multidimensional biological data to improve precision diagnosis and personalized patient management [5].

Artificial Intelligence in Precision Diagnosis

Artificial Intelligence (AI) has emerged as a transformative technology capable of revolutionizing the diagnosis and management of complex diseases such as PPCS. AI encompasses machine learning, deep learning, natural language processing, computer vision, and predictive analytics, enabling the extraction of clinically meaningful information from large and heterogeneous datasets [4]. Unlike conventional statistical methods, AI algorithms continuously learn from new information and improve diagnostic performance over time. By integrating clinical records, laboratory investigations, imaging studies, genomic profiles, wearable sensor data, and patient-reported outcomes, AI provides a comprehensive understanding of disease complexity. Machine learning algorithms can classify patients into distinct biological subgroups based on multidimensional biomarker profiles rather than symptom severity alone. This stratification facilitates personalized therapeutic selection and improves clinical decision-making.

Deep learning techniques have demonstrated exceptional performance in analysing radiological images, pulmonary computed tomography (CT), magnetic resonance imaging (MRI), echocardiography, and neurological imaging. AI-assisted image analysis detects subtle structural abnormalities that may escape conventional human interpretation. Natural language processing enables automated extraction of valuable clinical information from electronic health records, physician notes, discharge summaries, and patient-reported symptom diaries [6]. This capability significantly enhances large-scale epidemiological research and clinical surveillance. Importantly, AI systems can continuously monitor patient progress through wearable biosensors, mobile health applications, and cloud-based healthcare platforms in Figure 2. Continuous monitoring allows early identification of clinical deterioration, facilitating timely intervention and reducing healthcare burden.

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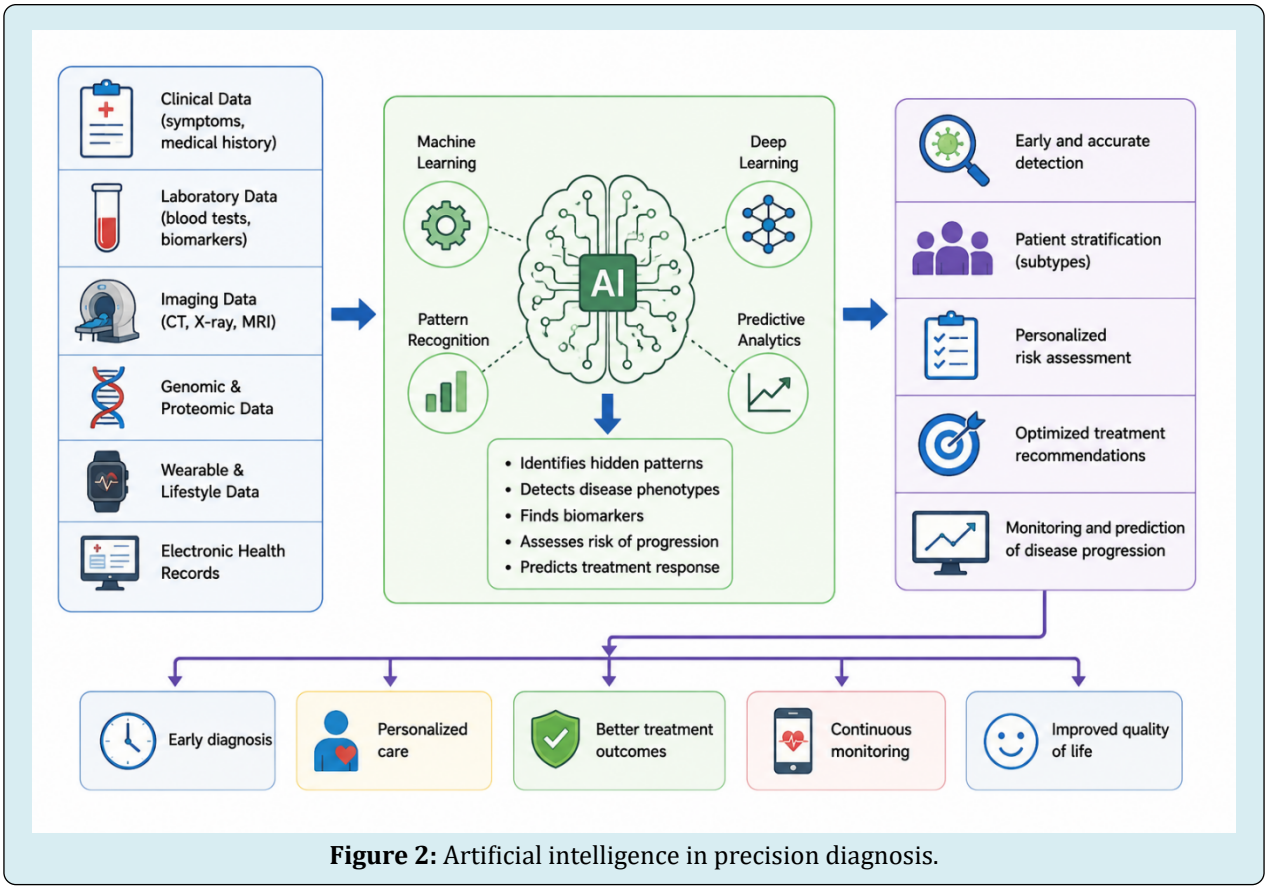


Figure 2: Artificial intelligence in precision diagnosis.

Machine Learning for Disease Prediction and Patient Stratification

Machine learning algorithms represent one of the most powerful components of AI-driven precision medicine. These algorithms identify hidden relationships within large datasets and generate predictive models capable of supporting individualized patient care. Supervised learning techniques utilize labelled datasets to predict disease outcomes based on previously observed clinical patterns. Common algorithms include Random Forests, Support Vector Machines, Gradient Boosting, and Artificial Neural Networks. Unsupervised learning identifies naturally occurring patient clusters without predefined classifications [7]. This approach is particularly valuable for PPCS because patients exhibit considerable biological heterogeneity. Clustering algorithms may reveal previously unrecognized disease phenotypes requiring distinct therapeutic strategies. Reinforcement learning continuously improves treatment recommendations through iterative feedback, allowing adaptive therapeutic optimization during long-term patient follow-up.

AI-based predictive models may estimate:

- Risk of developing PPCS following acute infection.
- Probability of neurological complications.
- Cardiovascular risk.
- Expected duration of symptoms.
- Likelihood of therapeutic response.
- Risk of hospital readmission.
- Long-term functional recovery.

Ai-Assisted Biomarker Discovery

One of the greatest strengths of AI lies in its ability to identify novel biomarkers that remain undetectable using conventional statistical analyses. Modern biomedical research generates enormous quantities of data from genomics, transcriptomic, proteomics, metabolomics, lipid omics, microbiomes, and immune omics. Manual interpretation of these datasets is both time-consuming and computationally challenging. AI algorithms rapidly integrate these multidimensional datasets, identifying molecular signatures associated with disease severity, immune dysfunction, and therapeutic response [8].

Potential biomarkers include:

- Cytokine signatures.
- Autoantibody profiles.
- MicroRNA expression.
- Extracellular vesicles.
- Metabolic fingerprints.

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- Immune cell phenotypes.
- Oxidative stress markers.
- Endothelial injury biomarkers.

Once identified, these biomarkers may guide the design of intelligent nanoparticle systems capable of delivering therapeutics directly to specific molecular targets, thereby improving efficacy while minimizing systemic toxicity [9]. AI-assisted biomarker discovery also supports precision patient stratification, enabling individualized treatment protocols tailored to each patient's unique biological profile in Table 2.

Nanoparticle Type	Characteristics	Potential Application in PPCS
Lipid nanoparticles	High biocompatibility	Drug and mRNA delivery
Polymeric nanoparticles	Controlled drug release	Long-term therapeutic delivery
Gold nanoparticles	Excellent imaging capability	Bio sensing and diagnostics
Magnetic nanoparticles	External magnetic guidance	Targeted drug delivery
Dendrimers	High drug-loading capacity	Gene and drug delivery
Exosome-based nanoparticles	Natural cellular communication	Immune modulation and tissue regeneration

Table 2: Types of Intelligent Nanoparticles and Their Biomedical Application [10].

Intelligent Nanoparticle Engineering

Intelligent nanoparticle engineering represents a significant advancement in precision Nano medicine through the development of multifunctional Nano systems capable of targeted diagnosis and therapy. These nanoparticles can be engineered with specific physicochemical properties, including particle size, surface charge, morphology, and biocompatibility, to enhance therapeutic efficacy while minimizing systemic toxicity. Surface functionalization with ligands, antibodies, or peptides enables selective recognition of diseased tissues and immune cells. Furthermore, stimuli-responsive nanoparticles can release therapeutic agents in response to changes in pH, temperature, enzymatic activity, or inflammatory biomarkers. Such intelligent Nano systems provide a promising platform for improving targeted interventions in Persistent Post-COVID Syndrome [11].

AI-Guided Nanoparticle Design

Artificial intelligence has revolutionized nanoparticle engineering by enabling rapid optimization of nanoparticle composition, structural characteristics, and therapeutic performance. Machine learning algorithms analyse extensive experimental datasets to predict particle stability, bio distribution, drug-loading efficiency, and potential toxicity before laboratory synthesis. AI-driven computational modelling significantly reduces research time, development costs, and experimental failures while accelerating the discovery of highly efficient Nano therapeutic systems. Predictive algorithms also facilitate personalized nanoparticle design based on patient-specific molecular and immunological profiles [12]. Consequently, AI-guided nanoparticle engineering enhances the precision, safety, and clinical applicability of next-generation Nano medicine.

Smart Nano Carriers for Drug Delivery

Smart Nano carriers have emerged as highly efficient drug delivery platforms capable of transporting therapeutic agents directly to diseased tissues with remarkable precision. These Nano carriers protect encapsulated drugs from premature degradation, improve bioavailability, and provide controlled or sustained drug release. Advanced Nano carrier systems including liposomes, polymeric nanoparticles, dendrimers, lipid nanoparticles, and exosomes can effectively deliver anti-inflammatory agents, antioxidants, nucleic acids, and immunomodulatory compounds [13]. Their targeted delivery minimizes off-target effects and reduces systemic toxicity. In Persistent Post-COVID Syndrome, smart Nano carriers offer significant potential for restoring immune homeostasis and improving therapeutic outcomes.

Immune Modulation Using Nanotechnology

Nanotechnology provides innovative strategies for regulating dysregulated immune responses associated with Persistent Post-COVID Syndrome. Engineered nanoparticles can selectively interact with immune cells, modulate cytokine production, reduce chronic inflammation, and restore immune equilibrium. Nanoparticle-mediated delivery of immunomodulatory agents, small interfering RNA (siRNA), messenger RNA (mRNA), peptides, or antioxidants enables highly targeted therapeutic interventions with minimal adverse effects. Additionally, nanoparticle-based immunotherapies may promote tissue repair, reduce oxidative stress, and enhance cellular regeneration. These multifunctional approaches represent a promising avenue for addressing the complex immunopathology underlying Long COVID [14].

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AI Nanoparticle Integration for Personalized Therapeutics

The integration of artificial intelligence with intelligent nanoparticle engineering represents a paradigm shift toward personalized therapeutics in Persistent Post-COVID Syndrome. AI algorithms analyse multidimensional clinical, immunological, genomic, and imaging data to identify individualized disease patterns and optimize therapeutic strategies. Based on these insights, intelligent nanoparticles can be engineered to deliver targeted drugs, nucleic acids, or immunomodulatory agents with high precision. AI further predicts nanoparticle bio distribution, therapeutic efficacy, and potential toxicity, enabling safer and more effective treatment planning. [15]. This synergistic approach enhances treatment accuracy, minimizes adverse effects, and supports adaptive, patient-specific therapeutic interventions. Consequently, AI nanoparticle integration has the potential to redefine precision medicine and improve long-term clinical outcomes in PPCS [16].

Clinical Translation and Future Perspectives

The successful clinical translation of AI-enabled intelligent nanoparticle systems requires multidisciplinary collaboration among clinicians, biomedical engineers, nanotechnologists, computational scientists, and regulatory authorities. Standardization of nanoparticle synthesis, validation of AI algorithms, large-scale clinical trials, and long-term safety assessments are essential before routine clinical implementation [17]. Future advancements are expected to integrate multi-omics technologies, wearable biosensors, digital twins, and real-time health monitoring with AI-driven Nano medicine to achieve highly personalized healthcare. Ethical considerations, data security, regulatory compliance, and equitable access to advanced technologies must also be addressed. Continued innovation in computational modelling and intelligent biomaterials will accelerate the development of next-generation therapeutic platforms in Table 3. These advances are expected to transform the diagnosis, monitoring, and treatment of Persistent Post-COVID Syndrome.

Emerging Technology	Potential Clinical Impact
Precision medicine	Individualized treatment strategies
Multi-omics integration	Biomarker-guided therapy
Digital twin technology	Virtual therapeutic simulation
Wearable biosensors	Continuous patient monitoring
Smart nanorobotics	Autonomous targeted drug delivery
Explainable AI	Transparent clinical decision-making
Internet of Medical Things (IoMT)	Remote healthcare management
Personalized Nano medicine	Improved long-term clinical outcomes

Table 3: Future Perspectives of AI-Enabled Intelligent Nanoparticle Therapeutics.

Conclusion

Persistent Post-COVID Syndrome remains a complex multisystem disorder with significant diagnostic and therapeutic challenges due to its heterogeneous clinical presentation and underlying biological mechanisms. The convergence of artificial intelligence and intelligent nanoparticle engineering offers an innovative precision medicine framework capable of improving early diagnosis, immune modulation, targeted drug delivery, and personalized therapeutics. AI-driven computational analysis combined with multifunctional Nano platforms enables individualized treatment strategies while enhancing therapeutic efficacy and reducing systemic toxicity [18]. Furthermore, the integration of multi-omics technologies, biosensors, and predictive analytics has the potential to revolutionize long-term disease monitoring and clinical decision-making. Although several scientific, regulatory, and ethical challenges remain, continued interdisciplinary research and technological innovation are expected to facilitate successful clinical translation. Ultimately, AI-enabled intelligent nanoparticle engineering represents a promising next-generation translational medicine approach for improving patient outcomes and quality of life in individuals affected by Persistent Post-COVID Syndrome.

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