**DERLEME**

# Kişiselleştirilmiş Egzersiz Reçetesinde Genetik, Epigenetik ve Yapay Zeka Tabanlı Biyobelirteçlerin Entegrasyonu

*Muhammed Celal ERYILMAZ*

## ÖZ

Geleneksel nüfus temelli modeller, temel olmakla birlikte; rehabilitasyon sonuçlarını şekillendiren biyolojik ve işlevsel heterojenliği yeterince yansıtmamaktadır. Genetik ve epigenetik araştırmalardaki ilerlemeler, kas performansını etkileyen gen polimorfizmleri ve egzersizin neden olduğu DNA metilasyonu veya miRNA yeniden modellenmesi gibi, adaptasyon ve iyileşmede bireyler arası değişkenliğin temelini oluşturan mekanik yolları ortaya çıkarmıştır. Bu moleküler bilgiler, yapay zeka destekli analitiklerle birleştirildiğinde, dinamik, veriye dayalı kişiselleştirilmiş tedaviye olanak tanır. YZ ve makine öğrenimi, giyilebilir sensörler, görüntüleme ve elektronik sağlık kayıtlarından elde edilen multimodal veri entegrasyonu yoluyla klinik tahmin, gerçek zamanlı izleme ve uyarlanabilir reçete yazımını geliştirir. Bu tür sistemler, egzersiz yoğunluğunun, ilerlemesinin ve geri bildirimin sürekli kalibrasyonuna olanak tanıyarak, klinisyenlerin gözetimini sürdürürken kişiselleştirilmiş bakımı tele-rehabilitasyon bağlamlarına genişletir. Ortopedi, nöroloji ve kronik ağrı alanlarında, randomize genotip veya epigenotip kılavuzlu çalışmalar sınırlı kalmakla birlikte, mevcut kanıtlar bu yaklaşımların translasyonel uygulanabilirliğini desteklemektedir. Etik uygulama, önyargıyı azaltmak ve hasta özerkliğini korumak için şeffaf yönetişim, genomik veri kullanımı için rıza ve adalet bilincine sahip YZ tasarımı gerektirir. Literatür, YZ'yı klinik uzmanlığın yerine geçmeyen bir yardımcı olarak tutarlı bir şekilde vurgulamakta ve biyobelirteçlere dayalı önerilerin yorumlanmasında insan yargısının merkezi rolünü pekiştirmektedir. İleride, biyolojik ve dijital olarak kişiselleştirilmiş rehabilitasyonun geleneksel protokollerin ötesinde sonuçları iyileştirip iyileştirmediğini doğrulamak için titizlikle tasarlanmış, etik temelli denemeler gereklidir. Bireyselleştirilmiş rehabilitasyon, bu nedenle, daha etkili ve eşitlikçi fizik tedavi arayışında moleküler içgörü, hesaplamalı zeka ve hasta merkezli bakımı birleştiren hem bilimsel hem de etik bir öncüldür.

**Anahtar Kelimeler:** Bireyselleştirilmiş Tıp; Fizik tedavi modaliteleri; Genomlar; Rehabilitasyon; Yapay zeka

# Integration of Genetic, Epigenetic and Artificial Intelligence-Based Biomarkers in Personalized Exercise Prescription

*Muhammed Celal ERYILMAZ*

## ABSTRACT

Traditional population-based models, while foundational, inadequately capture the biological and functional heterogeneity that shapes rehabilitation outcomes. Advances in genetic and epigenetic research have revealed mechanistic pathways such as gene polymorphisms influencing muscle performance and exercise-induced DNA methylation or miRNA remodeling that underpin interindividual variability in adaptation and recovery. These molecular insights, when coupled with AI-driven analytics, enable dynamic, data-informed personalization of therapy. AI and machine learning enhance clinical prediction, real-time monitoring, and adaptive prescription through multimodal data integration from wearable sensors, imaging, and electronic health records. Such systems allow continuous calibration of exercise intensity, progression, and feedback, extending personalized care into tele-rehabilitation contexts while maintaining clinician oversight. Across orthopedic, neurological, and chronic pain domains, current evidence supports the translational feasibility of these approaches, though randomized genotype- or epigenotype-guided trials remain limited. Ethical implementation requires transparent governance, consent for genomic data use, and fairness-aware AI design to mitigate bias and protect patient autonomy. The literature consistently underscores AI as an adjunct, not a substitute for clinical expertise, reinforcing the centrality of human judgment in interpreting biomarker-informed recommendations. Moving forward, rigorously designed, ethically grounded trials are essential to validate whether biologically and digitally personalized rehabilitation improves outcomes beyond conventional protocols. Precision rehabilitation thus represents both a scientific and ethical frontier, uniting molecular insight, computational intelligence, and patient-centered care in the pursuit of more effective and equitable physical therapy.

**Keywords:** Artificial intelligence; Genomics; Physical therapy modalities; Precision medicine; Rehabilitation

**Sorumlu Yazar**: Muhammed Celal ERYILMAZ
**E-posta adresi:** muhammedceryilmaz@gmail.com **ORCID No:** 0009-0000-3448-2536
**Gönderi Tarihi:** 04.11.2025 **Kabul Tarihi:** 27.02.2026

## INTRODUCTION

Exercise prescription in physical therapy has evolved from generalized, population-based protocols toward increasingly individualized approaches. Historically, standardized regimens were developed to provide consistency and safety, yet these "one-size-fits-all" methods overlook substantial inter-individual variability in functional adaptation, recovery trajectories, and long-term outcomes (1, 2). Emerging work emphasizes that such uniformity limits the optimization of therapeutic intensity, progression, and modality for diverse patient populations (3, 4). Precision rehabilitation proposes to overcome these shortcomings through person-specific assessments that integrate biological, behavioral and environmental factors (5). High-resolution studies in pediatric and neurorehabilitation contexts have shown that individualized measurement of motor learning, dosage and progression rules can enhance responsiveness and outcomes (5). Taken together, these advancements represent a fundamental shift from standardized exercise protocols toward a paradigm of care that is both biologically grounded and dynamically adaptive.

The incorporation of precision-medicine principles into physical therapy reflects a paradigm shift from population averages to individualized optimization of rehabilitation. By leveraging genetic, epigenetic, and phenotypic information, clinicians can better predict and monitor exercise responses, tailoring interventions to maximize efficacy and minimize risk (2, 6). Genetic variation such as polymorphisms in the ACE gene has been associated with differences in strength and endurance adaptations, suggesting that genotype-informed prescriptions could refine rehabilitation programming (7). Complementarily, exercise-induced epigenetic remodeling, including changes in DNA methylation, histone modifications, and microRNA expression, provides a mechanistic link between training stimuli and durable physiological adaptations (8, 9). AI-driven analytics further enable the integration of multiomics, wearable, and digital health data to generate predictive biomarkers and guide ongoing adjustments to individualized exercise plans (10-12). In practice, digital therapeutics and shared decision-making platforms extend these insights to routine care, aligning biological precision with patient-centered goals.

This review synthesizes current evidence on the convergence of genetics, epigenetics, and artificial intelligence in shaping precision rehabilitation. This work outlines the historical progression of exercise prescription while addressing the shortcomings of traditional paradigms; furthermore, it explores the potential of integrated biological and computational data in predicting individual responsiveness to exercise. The goal is to articulate an integrative framework for precision rehabilitation linking baseline molecular profiling, AI-driven biomarker discovery, and adaptive, patient-centered exercise prescription while highlighting practical considerations such as data privacy, clinician education, and the need for longitudinal validation.

## METHODS

### Study Design

This study was conducted as a narrative review with a translational and exploratory orientation. The primary aim was not to perform a systematic comparison of intervention effectiveness or to generate pooled effect estimates, but rather to conceptually integrate biological, molecular, and computational evidence relevant to precision rehabilitation in physical therapy. Accordingly, the review focuses on mechanistic plausibility, emerging translational frameworks, and clinically relevant applications of genetics, epigenetics, and artificial intelligence in individualized exercise prescription.

### Literature Search Strategy

A structured narrative literature search was undertaken to identify peer-reviewed studies addressing biological and digital determinants of exercise response and rehabilitation personalization. The databases PubMed/MEDLINE, Scopus, Web of Science and IEEE Xplore were searched to reflect both biomedical and engineering-oriented rehabilitation research.

Based on the temporal distribution of the included literature, the search encompassed publications from January 2020 to March 2025, corresponding to the period in which precision medicine concepts, exercise genomics/epigenetics and AI-enabled rehabilitation technologies began to converge within physical therapy research.

Search terms were combined using Boolean operators and included: physical therapy, rehabilitation, exercise prescription, precision rehabilitation, genetics, genomics, epigenetics, microRNA, artificial intelligence, machine learning, wearable sensors, biomechanics, robot-assisted rehabilitation and digital therapeutics. In addition, the reference lists of key narrative reviews, consensus statements and translational frameworks were manually screened to identify relevant studies not captured in the initial database search.

**Eligibility Criteria and Study Selection**

Eligible publications included original research articles, systematic or narrative reviews, translational studies, methodological frameworks and consensus statements that addressed at least one of the following domains:

(i) genetic or epigenetic mechanisms underlying exercise adaptation or rehabilitation response;

(ii) AI- or machine learning–based assessment, monitoring or personalization strategies in rehabilitation;

(iii) integrative precision medicine approaches applicable to physical therapy practice.

Studies were excluded if they were not published in English, lacked full-text availability, or focused exclusively on pharmacological interventions or non-therapeutic exercise contexts. Conference abstracts without peer-reviewed full manuscripts were also excluded. Given the narrative design, study selection emphasized conceptual relevance, mechanistic insight, and translational applicability, rather than adherence to a predefined hierarchy of clinical evidence.

**Data Extraction and Synthesis**

From each included study, information was extracted regarding study focus, biological or computational mechanisms, rehabilitation context, and implications for individualized exercise prescription. Findings were synthesized qualitatively rather than quantitatively, allowing identification of thematic convergence across genetic, epigenetic and AI-driven domains.

Evidence was interpreted along a translational continuum, distinguishing exploratory mechanistic findings from clinically applicable frameworks.

This integrative approach supported the development of a conceptual model linking molecular profiling, AI-assisted data integration, and adaptive, patient-centered rehabilitation strategies, while remaining aligned with the scope and evidentiary boundaries of the existing literature.

## BIOLOGICAL DETERMINANTS OF EXERCISE RESPONSE

Individual variability in exercise adaptation reflects genetic influences that shape muscle, cardiovascular, and connective tissue responses to training. Variants in genes such as ACTN3 and ACE have been associated in broader exercise-science literature with differences in muscle strength, hypertrophy, and aerobic capacity, suggesting that genotype may partly determine rehabilitation response potential (2). While the provided corpus does not present primary data linking these polymorphisms directly to physical therapy outcomes, it emphasizes precision medicine frameworks that advocate integrating genetic and molecular data into individualized rehabilitation planning (2, 5, 13). Genetic variation may also influence tissue resilience: polymorphisms affecting collagen synthesis and extracellular matrix regulation could modulate susceptibility to tendinopathy and ligament injury, highlighting a genetic substrate for tailored loading and recovery strategies (14). Overall, genetic information represents a foundational, though currently undervalidated, axis for predicting exercise response and injury risk in precision physical therapy.

Exercise induces both acute and long-term molecular adaptations through epigenetic remodeling, including DNA methylation and histone modifications that regulate gene expression in muscle, tendon and vascular tissues (14, 15). These changes underpin tissue repair, angiogenesis, and metabolic remodeling, providing potential biomarkers for adaptive capacity and recovery monitoring. Epigenetic regulation is particularly evident in tendon and endothelial biology, where mechanical loading alters cytokine expression, extracellular matrix composition and vascular protective pathways (14, 15). MicroRNAs (miRNAs), key post-transcriptional regulators of gene expression, also contribute to muscle plasticity, coordinating the processes of repair, hypertrophy and degeneration following exercise. Although the current references do not include direct empirical evidence on miRNA-specific adaptations, they situate such mechanisms within the broader context of exercise-induced molecular signaling and immunometabolic regulation (16). Together, these pathways are summarized conceptually in Figure 1, which illustrates the integration of genetic and epigenetic factors shaping adaptive and rehabilitative outcomes.

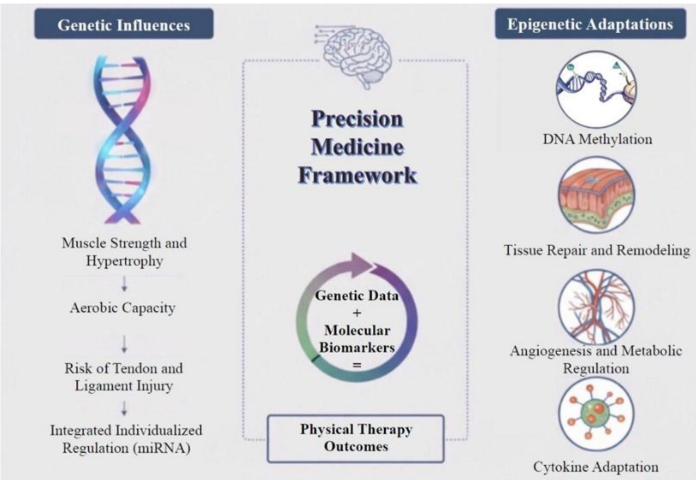


**Figure 1.** Genetic and epigenetic regulation of exercise adaptation and rehabilitation potential.

## PERSONALIZATION WITH ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

AI and ML frameworks facilitate the early identification of non-response risks by synthesizing demographic profiles, comorbidities, and baseline functional metrics. By preemptively identifying patients unlikely to benefit from standard protocols, these models allow clinicians to refine treatment trajectories, thereby optimizing dosage and progression while reducing therapeutic inefficiency (17–19). Notably, in stroke and robotic rehabilitation, such systems integrate multi-domain data streams (including clinical and sensor-derived inputs) to forecast functional outcomes and inform adaptive therapy scheduling (18, 20).

Wearable sensors such as Inertial Measurement Unit (IMUs), accelerometers, and camera-based systems generate continuous biomechanical and behavioral data that quantify exercise compliance, dosage, and performance. Deep-learning algorithms process these large datasets to recognize movement patterns, track adherence, and inform real-time progression or regression of exercises (21-23). Remote monitoring frameworks extend these capabilities to home-based settings, supporting tele-rehabilitation and continuous feedback loops for adaptive, data-driven exercise prescription (20).

AI facilitates biomechanically informed prescriptions by identifying subtle deviations in gait, posture, and movement execution, biomechanical biomarkers that reflect neuromuscular control and recovery status (24, 25). These insights enable targeted exercise selection and progression criteria aligned with objective performance metrics. Deep-learning systems further support dynamic adjustment of therapy variables including intensity, sets and repetitions based on real-time feedback, ensuring safe, responsive, and personalized progression (18, 26, 27). Together, these AI-driven approaches integrate prediction, monitoring, and adaptive prescription to realize the vision of precision physical therapy through continuous clinician–AI collaboration (19, 24, 28) (Figure 2).

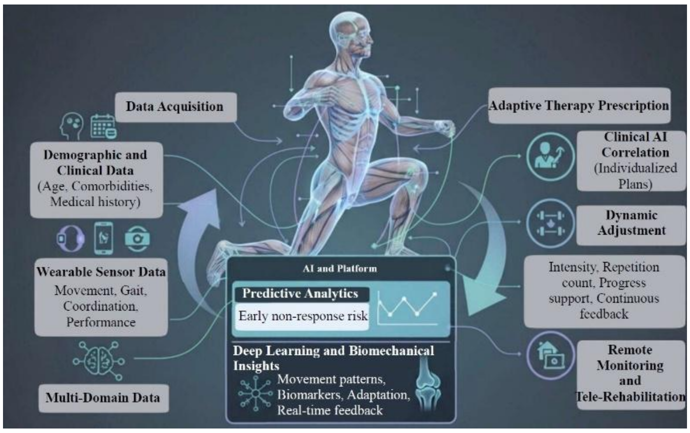


**Figure 2.** Precision physical therapy: a closed-loop AI framework.

## CLINICAL APPLICATION AREAS AND LEVEL OF EVIDENCE

In orthopedic rehabilitation, integrating genetic, epigenetic, and AI-derived biomarkers offers a framework for individualized postoperative and musculoskeletal system care. Epigenetic mechanisms translate exercise and environmental influences into durable biological adaptations relevant to post–Total Knee Arthroplasty (TKA) recovery (1). Although direct genotype-guided TKA protocols are not yet established, genomic testing has been proposed to inform rehabilitation planning, providing a conceptual model for personalized loading and progression (29). Mechanistic and translational studies on electrically induced exercise further demonstrate how genomic and epigenomic remodeling underpins muscular and neural adaptations (3). AI-enabled analytics can operationalize these insights by merging biomarker, biomechanical, and performance data to support real-time decision-making in orthopedic rehabilitation (30, 31).

In chronic low back pain (LBP), genetic and epigenetic variations influence pain perception, tissue adaptation, and recovery potential (32).

Epigenetic regulation of tendon and extracellular matrix remodeling highlights a biological basis for tailoring loading schemes (14). AI-driven rehabilitation systems facilitate integration of biomarker, movement, and patient-reported data into adaptive, measurement-based care (5, 13, 31). Despite this mechanistic promise, genotype- and epigenotype-guided personalization in LBP remains at an exploratory stage, with robust evidence currently limited to the efficacy of exercise and education interventions from meta-analyses and clinical guidelines (33-36).

For anterior cruciate ligament (ACL) reconstruction, current work emphasizes AI-augmented biomechanical optimization, gait analysis, and precision dosing (30, 37). However, no ACL-specific genotype or epigenotype studies are reported in the cited sources. Thus, personalization remains conceptual and translational, grounded in AI-assisted motor learning and movement analytics rather than genomic evidence. Across orthopedic domains, the overall evidence level for genotype- and epigenotype-informed rehabilitation is translational and exploratory, supported by mechanistic rationale but lacking randomized genotype-guided trials.

In neurological rehabilitation, genotype- and epigenotype-informed exercise interventions remain largely theoretical but mechanistically supported. Epigenetic and genomic modulation of exercise responses in neuromuscular tissues provides a foundation for designing individualized motor-learning protocols (3). These studies show that electrical or exercise-induced activation can reprogram gene expression in muscle–nerve units, offering a biological substrate for recovery strategies in stroke and Parkinson's disease (PD). Exercise-induced neuroplasticity further supports the rationale for targeted rehabilitation that enhances motor control and learning (38).

AI-enabled neurorehabilitation systems are emerging as integrative platforms capable of aligning molecular and biomechanical data with adaptive training protocols (31). However, within the provided references, no randomized genotype-guided stroke or PD trials exist. The current evidence is therefore exploratory and translational, offering mechanistic plausibility but awaiting clinical validation through prospective studies integrating omics, neuroplasticity markers, and AI-driven decision support.

**Table 1.** Cross-Domain Translational Framework Integrating Biological and Artificial Intelligence–Driven Evidence in Major Rehabilitation Fields.

| Rehabilitation Clinical Domain | Dominant Evidence Layer | Consistent Findings Across Studies | Cross-Study Pattern & Interpretation | Methodological Constraints | Clinical & Translational Implications for Physical Therapy |
|---|---|---|---|---|---|
| Orthopedic Rehabilitation | Exercise genomics, skeletal muscle and tendon epigenetics, AI-based biomechanical analytics | Genetic polymorphisms influence strength and hypertrophy responses; epigenetic markers are responsive to mechanical loading; AI enhances precision in movement analysis | Genetic factors explain baseline interindividual variability, whereas epigenetic mechanisms demonstrate greater responsiveness to exercise stimuli; AI provides immediate functional translation | Predominantly associative genetic evidence; limited longitudinal epigenetic studies; heterogeneous AI validation | Enables individualized loading strategies, adaptive progression, and data-informed return-to-activity decisions |
| Neurological Rehabilitation | Epigenetic modulation of neuroplasticity, genomics-informed exercise, AI-driven motor recovery modeling | Exercise induces molecular and epigenetic signatures linked to neural plasticity; AI systems predict functional recovery trajectories | Epigenetic mechanisms mediate the interaction between task-specific training and recovery; AI accelerates clinical decision-making | Limited integration of molecular outcomes into clinical trials; small sample sizes | Informs task-specific intensity dosing and adaptive neurorehabilitation strategies |
| Cardiopulmonary Rehabilitation | Exercise genomics, cardiovascular epigenetics, AI-supported physiological monitoring | Large variability in aerobic adaptation; epigenetic responses contribute to vascular and cardiac health; AI improves monitoring and shared decision-making | Genetic contribution is partial; dynamic physiological data offer stronger immediate translational value | Lack of genotype-based prescription thresholds; data governance challenges | Supports precision aerobic prescription and real-time risk-adaptive progression |
| Musculoskeletal Pain Rehabilitation | Epigenetic regulation of inflammation and pain sensitivity, AI-based pain phenotyping, digital therapeutics | Exercise modulates inflammatory and neuroplastic pathways; AI identifies responder subgroups and optimizes intervention matching | Epigenetic plasticity underlies exercise-induced analgesia; AI enables stratified and adaptive care | Predominantly correlational data; limited mechanistic and longitudinal studies | Facilitates tailored exercise selection, dosage modulation, and expectation management |
| Sports Rehabilitation & Performance-Oriented Rehab | Polygenic performance profiles, multiomics exercise responses, AI-based workload and fatigue modeling | Multimodal models outperform single-domain prediction for performance and injury risk | Integration of biological and AI-derived data yields superior predictive capacity; AI shows highest translational readiness | Elite-athlete bias; limited transferability to general clinical populations | Bridges elite sports science and clinical FTR through individualized load management |
| Geriatric Rehabilitation | Epigenetic aging markers, AI-driven functional decline and fall-risk prediction | Exercise influences biological aging signatures; AI predicts functional deterioration and fall risk | Epigenetic age appears modifiable through lifestyle interventions; AI enables early preventive strategies | Underrepresentation of frail elderly; short follow-up durations | Supports precision balance training, fall prevention, and functional preservation |

Genetic influences on pain perception, such as brain-expressed gene variants associated with chronic back pain, provide a biologic rationale for integrating genotype data into pain-focused rehabilitation (32). Sports genomics research similarly links genetic markers to injury risk and recovery potential, supporting the conceptual use of gene-informed strategies in chronic musculoskeletal pain (39). Epigenetic frameworks also explain how behavioral and environmental inputs can yield sustained functional changes through gene regulation, aligning with biopsychosocial rehabilitation models (1).

AI-enabled precision rehabilitation provides practical tools for continuous monitoring and adaptive management of pain-related outcomes by integrating sensor data, biomarker inputs, and contextual variables (30, 31). Nonetheless, current high-quality evidence supports exercise and education as the primary interventions for chronic pain (33-36). Genotype- and epigenotype-guided personalization remains observational and mechanistic, with promising translational pathways but no definitive clinical efficacy demonstrated in randomized trials.

To enable a structured and clinically meaningful synthesis, Table 1 integrates genetic, epigenetic, and artificial intelligence–driven evidence across major rehabilitation domains, highlighting cross-domain patterns, methodological constraints, and translational implications for physical therapy.

## DISCUSSION

Integrating genomic, epigenetic, and digital biomarkers into physical therapy (PT) promises a new level of personalization but introduces significant ethical and methodological demands. Contemporary frameworks propose merging multiomics profiles with wearable-derived kinematic and functional data to refine exercise dosing and progression (19, 20, 23, 28, 29). Successful implementation depends on standardized pipelines for data collection, interoperability, and transparent mapping of biomarker signals to clinical outcomes (5, 40).

Ethically, the integration of genomic data raises enduring challenges: privacy, informed consent, incidental findings, data reuse, and equitable access (40, 41). Protocol-level models such as EXESALUS illustrate how genomic testing can be embedded within exercise programs, emphasizing robust consent, governance of data reuse, and continuous oversight (29). Equity considerations remain paramount: AI-enabled rehabilitation could exacerbate disparities unless systems are validated across sex, age, ethnicity, and comorbidity profiles (40, 42). Consensus statements therefore urge fairness-aware AI design and inclusive genomic sampling to prevent bias (41).

Overall, the literature positions AI and genomics as complementary components of an ethically governed, clinician-led ecosystem. Implementation should proceed through transparent consent models, rigorous data stewardship and phased pilot trials before routine deployment (29, 40, 41).

Across recent studies, AI is consistently characterized as an enhancer of clinical expertise rather than a replacement. Machine learning and robotic systems enable data-rich precision in assessment, dosing, and monitoring while preserving the central role of human reasoning and empathy (5, 13, 19, 28). AI-driven robotics, wearable sensing, and computer-vision systems allow near real-time adjustment of exercise intensity and feedback under clinician supervision (23-25). These technologies expand measurement-based care and tele-rehabilitation capacity without displacing professional oversight (20, 43).

However, overreliance on opaque algorithms risks bias and erosion of trust. Authors emphasize “human-in-the-loop” frameworks that ensure explainable AI and maintain clinician accountability in interpreting biomarker-informed recommendations (13, 44). This transition requires workforce upskilling in AI literacy, data ethics, and biomarker interpretation (30, 31). Patient-centered design: explicit education about AI’s role, informed consent for data use, and transparency about algorithmic limits remains vital to sustaining the therapeutic alliance (40, 41). Thus, AI’s future in PT lies in clinician–technology synergy, augmenting decision-making and extending access to high-quality, individualized care.

While translational studies confirm the biological plausibility of genotype-/epigenotype-informed rehabilitation, high-quality RCTs remain scarce. Mechanistic evidence demonstrates exercise-induced gene regulation and epigenetic adaptation in muscle and tendon (1, 14, 45, 46), yet no large trials have compared biomarker-guided protocols to conventional care across orthopedic, neurologic, or chronic pain contexts (29, 41). Foundational frameworks such as the "Systems Exercise Genetics Research Design Standards" (40) provide methodological blueprints for such trials emphasizing standardized biospecimen collection, cross-site harmonization, and transparent reporting. A phased trial model is proposed: feasibility studies validating biomarker measurement in PT settings; pilot RCTs testing genotype-/epigenotype-informed prescriptions (e.g., post-ACL or chronic LBP) against guideline-based care; and multi-site, adequately powered trials incorporating subgroup analyses by genotype, sex, and ethnicity (2, 33). Each phase must embed ethical and governance safeguards, including consent for genetic data and AI explainability to preserve clinician oversight (13, 41).

Current evidence is largely exploratory or in the early translational stages. Consequently, the field must prioritize rigorously designed, ethically sound RCTs. By integrating genomic, epigenetic, and AI-driven biomarkers, these studies should evaluate whether personalized prescriptions offer superior clinical and biological outcomes (29, 40, 41).

**Limitations**

This review is subject to several limitations inherent to the current evidence base. First, substantial heterogeneity across genetic, epigenetic, and artificial intelligence–driven studies limited direct comparability and precluded quantitative synthesis, necessitating a narrative, framework-based approach. Second, much of the biological evidence remains associative, restricting causal inference and the immediate clinical application of molecular markers in physical therapy decision-making. Third, while artificial intelligence–based tools demonstrate promising translational potential, their generalizability is constrained by limited external validation and domain-specific datasets. Finally, the rehabilitation-domain–oriented framework adopted in this review prioritizes cross-domain synthesis and clinical relevance but may underrepresent condition-specific nuances. As the field evolves rapidly, the proposed framework should be interpreted as adaptive and subject to refinement as higher-quality and more integrative evidence emerges.

## CONCLUSION

The convergence of genomics, epigenetics, and artificial intelligence marks a transformative juncture in physical therapy, positioning the discipline at the forefront of precision medicine. By integrating multiomics data with digital biomarkers and AI-enabled analytics, clinicians can move beyond population-level protocols toward adaptive, biologically grounded interventions that reflect each patient's unique recovery potential. Yet, the realization of this vision depends on the maturation of both evidence and ethics. The current body of work underscores that while mechanistic and translational studies have elucidated the molecular underpinnings of exercise adaptation, robust randomized controlled trials are still required to demonstrate the superiority and safety of genotype- or epigenotype-informed rehabilitation. Equally critical is the establishment of governance frameworks that safeguard privacy, ensure fairness, and promote transparency in AI-supported decision-making.

Ultimately, the future of precision physical therapy will be defined not by technological sophistication alone but by the discipline's capacity to integrate innovation with human judgment, ethical stewardship, and empirical rigor. Clinician-led, AI-augmented systems offer a pathway to more responsive, equitable, and evidence-based care provided that research adheres to standardized design principles and patient-centered ethics. Through deliberate, multidisciplinary collaboration and rigorous clinical validation, precision rehabilitation can evolve from conceptual promise to clinical reality, advancing both the science and the humanity of therapeutic care.

## REFERENCES

1. Shields RK, Dudley-Javoroski S. Epigenetics and the International Classification of Functioning, Disability and Health model: bridging nature, nurture, and patient-centered population health. Phys Ther. 2022; 102(1): pzab247.
2. Severin R, Sabbahi A, Arena R, Phillips SA. Precision medicine and physical therapy: a healthy living medicine approach for the next century. Phys Ther. 2022; 102(1): pzab253.
3. Petrie MA, Taylor EB, Suneja M, Shields RK. Genomic and epigenomic evaluation of electrically induced exercise in people with spinal cord injury: application to precision rehabilitation. Phys Ther. 2022; 102(1): pzab243.
4. Egan B, Sharples AP. Molecular responses to acute exercise and their relevance for adaptations in skeletal muscle to exercise training. Physiol Rev. 2023; 103(3): 2057-2170.
5. Skorup JC, Pierce SR, Paremski AC, Alcott M, Prosser LA. Precision measurement of rehabilitation interventions: a secondary analysis of motor error in a clinical trial with young children with cerebral palsy. Front Pediatr. 2024; 12:1457329.
6. Rohaj A, Bulaj G. Digital therapeutics (DTx) expand multimodal treatment options for chronic low back pain: the nexus of precision medicine, patient education, and public health. Healthcare (Basel). 2023; 11(10):1469.
7. Sjúrðarson T, Nordsborg N. Angiotensin-converting enzyme and exercise adaptations: genetic variability, pharmacological modulation and future directions. J Physiol. 2025.
8. Krammer UDB, Sommer A, Tschida S, Mayer A, Lilja SV, Switzeny OJ, Hippe B, Rust P, Haslberger AG. PGC-1α methylation, miR-23a, and miR-30e expression as biomarkers for exercise- and diet-induced mitochondrial biogenesis in capillary blood from healthy individuals: a single-arm intervention. Sports (Basel). 2022; 10(5): 73.
9. Wu G, Zhang X, Gao F. The epigenetic landscape of exercise in cardiac health and disease. J Sport Health Sci. 2021; 10(6): 648–659.

10. Zhao X, Nie X. Subgroup state prediction under different noise levels using MODWT and XGBoost. J Healthc Eng. 2023; 2023: 6406275.
11. Fan D, Yang X, Zhao N, Guan L, Abbasi QH. Exercise monitoring and assessment system for home-based respiratory rehabilitation. IEEE Sens J. 2022; 22(19): 18890–18902.
12. Kizilkilic SE, Ramakers W, Falter M, Scherrenberg M, Bonneux C, Pieters Z, Milani M, Hansen D, De Pauw M, Coninx K, Dendale P. A digitally-supported shared decision making approach for patients during cardiac rehabilitation: a randomized controlled trial. Eur J Prev Cardiol. 2025.
13. Mohapatra A, Mohanty P, Pattnaik M, Padhan S. Physiotherapy in the digital age: a narrative review of the paradigm shift driven by the integration of artificial intelligence and machine learning. Physiotherapy (Indian Assoc Physiotherapists). 2024; 18(2): 63–71.
14. Williams S, Ligas C, Oloff L, Klein TE. The role of epigenomics in mapping potential precursors for foot and ankle tendinopathy: a systematic review. Foot Ankle Spec. 2023; 16(4): 446–454.
15. Amador M, Huerta JA, Arias Garcia M, Conde D, Gurovich AN. In vitro exercise-induced endothelial shear stress protects the vascular endothelium. Cardiopulm Phys Ther J. 2022; 34: 81–86.
16. Wojciuk B, Frulenko I, Brodkiewicz A, Kita D, Baluta M, Jędrzejczyk F, Budkowska M, Turkiewicz K, Proia P, Ciechanowicz A, Kostrzewa-Nowak D, Nowak R. The complement system as a part of immunometabolic post-exercise response in adipose and muscle tissue. Int J Mol Sci. 2024; 25(21): 11608.
17. Rahman S, Sarker S, Haque AKMN, Uttsha MM, Islam MF, Deb S. AI-driven stroke rehabilitation systems and assessment: a systematic review. IEEE Trans Neural Syst Rehabil Eng. 2023; 31: 192–207.
18. Ai Q, Liu Z, Meng W, Liu Q, Xie SQ. Machine learning in robot-assisted upper limb rehabilitation: a focused review. IEEE Trans Cogn Dev Syst. 2023; 15(4): 2053–2063.
19. Baysal Z. AI-driven rehabilitation robots: enhancing physical therapy for stroke and injury recovery. Next Front Life Sci AI. 2024; 8(1): 155.
20. Narula S, Pol RS. Temporal multimodal fusion network for real-time patient monitoring in rehabilitation. J Inf Syst Eng Manag. 2025; 10 (23): 255-269.
21. Zhang W, Su C, He C. Rehabilitation exercise recognition and evaluation based on smart sensors with deep learning framework. IEEE Access. 2020; 8: 77561-77571.
22. Sitar EM, Saadat MS, Sur S. A millimeter-wave wireless sensing approach for at-home exercise recognition. In: Proceedings of the 20th Annual ACM International Conference on Mobile Systems, Applications and Services (MobiSys '22), Portland, Oregon, 27 June–1 July 2022. New York: ACM; 2022. p. 555-556.
23. Huang Y, Yang B, Wong TW, Ng SSM, Hu X. Personalized robots for long-term telerehabilitation after stroke: a perspective on technological readiness and clinical translation. Front Rehabil Sci. 2024; 4: 1329927.
24. Cirillo E, Conte C, Moccardi A, Fonisto M. Resilient AI in therapeutic rehabilitation: the integration of computer vision and deep learning for dynamic therapy adaptation. Appl Sci. 2025; 15(12): 6800.
25. Zhang X, Rong X, Luo H. Optimizing lower limb rehabilitation: the intersection of machine learning and rehabilitative robotics. Front Rehabil Sci. 2024; 5: 1246773.
26. Jiang Z, Wang Z, Lv Q, Yang J. Impedance learning-based hybrid adaptive control of upper limb rehabilitation robots. Actuators. 2024; 13(6): 220.
27. Xu C. Advancements of deep learning model-based rehabilitation training system. ITM Web Conf. 2025; 70: 02024.
28. Touhiduzzaman M, Hernandez SM, Pidcoe PE, Bulut E. Wi-PT-Hand: wireless sensing based low-cost physical rehabilitation tracking for hand movements. ACM Trans Comput Healthcare. 2025; 6(1): 12.
29. Choi Y, Jee H. The protocol for developing health and disease prevention services: an exercise-based prediction model integrating genomic test results. PLoS One. 2025; 20(7): e0327947.
30. Dergaa I, Chamari K. Big data in sports medicine and exercise science: integrating theory and practice for future innovations. Tunisian J Sports Sci Med. 2024; 2(1): 1–13.
31. Dubey A, Uldin H, Khan Z, Panchal H, Iyengar KP, Botchu R. Role of artificial intelligence in musculoskeletal interventions. Cancers. 2025; 17(10): 1615.
32. Bortsov AV, Parisien M, Khoury S, Zaykin DV, Martinsen AE, Lie MU, Heuch I, HUNT All-In Pain, Hveem K, Zwart JA, Winsvold BS, Diatchenko L. Genome-wide analysis identifies significant contribution of brain-expressed genes in chronic, but not acute, back pain. Pain Rep. 2021; 6: e1018.
33. Li Y, Yan L, Hou L, Zhang X, Zhao H, Yan C, Li X, Li Y, Chen X, Ding X. Exercise intervention for patients with chronic low back pain: a systematic review and network meta-analysis. Front Public Health. 2023; 11: 1155225.
34. Lara-Palomo IC, Antequera-Soler E, Matarán-Peñarrocha GA, Fernández-Sánchez M, García-López H, Castro-Sánchez AM, Aguilar-Ferrándiz ME. Comparison of the effectiveness of an e-health program versus a home rehabilitation program in patients with chronic low back pain: A double blind randomized controlled trial. Digit Health. 2022; 8: 20552076221074482.
35. Jones KC, Tocco EC, Marshall AN, Valovich McLeod TC, Welch Bacon CE. Pain education with therapeutic exercise in chronic nonspecific low back pain rehabilitation: a critically appraised topic. J Sport Rehabil. 2020; 29(8): 1204-1209.
36. Schmidt AM, Schiøttz-Christensen B, Foster NE, Laurberg TB, Maribo T. The effect of an integrated multidisciplinary rehabilitation programme alternating inpatient interventions with home-based activities for patients with chronic low back pain: a randomized controlled trial. Clin Rehabil. 2020; 34(3): 382-393.
37. T T EG, Dev M, Milton JA, K.V A, Manikantan M, Jacob MA. Comparative study on lumbar stabilization and dynamic lumbar strengthening exercises in reducing pain and disability for patients with chronic low back pain: experimental study. Physiotherapy. 2025;11(1): 2216–2230.
38. Zou J, Hao S. Exercise-induced neuroplasticity: a new perspective on rehabilitation for chronic low back pain. Front Mol Neurosci. 2024; 17: 1407445.
39. Ginevičienė V, Utkus A, Pranckevičienė E, Semenova EA, Hall ECR, Ahmetov II. Perspectives in sports genomics. Biomedicines. 2022; 10(2): 298.
40. Lightfoot J, Roth S, Hubal M. Systems exercise genetics research design standards. Med Sci Sports Exerc. 2021; 53(5): 883–887.
41. Tanisawa K, Wang G, Seto J, Verdouka I, Twycross-Lewis R, Karanikolou A, et al. Sport and exercise genomics: the FIMS 2019 consensus statement update. Br J Sports Med. 2020; 54(16): 969–975.
42. Lavin K, O'Bryan S, Pathak K, Garcia-Mansfield K, Graham Z, McAdam J, et al. Divergent multiomic acute exercise responses reveal the impact of sex as a biological variable. Physiol Genomics. 2025; 57(5): 321–342.
43. Gul S. Frontiers in neuromuscular physical therapy. Rehabil Commun. 2023; 2(1): 1–2.

44. Yang X, Li Y, Mei T, Duan J, Yan X, McNaughton L, et al. Genome-wide association study of exercise-induced skeletal muscle hypertrophy and the construction of predictive model. Physiol Genomics. 2024; 56(8): 578–589.
45. Guseh JS, Churchill TW, Yeri A, Lo C, Brown M, Houstis NE, Aragam KG, Lieberman DE, Rosenzweig A, Baggish AL. An expanded repertoire of intensity-dependent exercise-responsive plasma proteins tied to loci of human disease risk. Sci Rep. 2020; 10(1): 10831.
46. Watso J, Romero S, Moralez G, Huang M, Cramer M, Jaffery M, et al. Six months of exercise training improves ventilatory responses during exercise in adults with well-healed burn injuries. Med Sci Sports Exerc. 2022; 55 (5): 765–776.