Review Article

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AI Applications in Diagnosing Rare Genetic Disorders

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Received: 06 November 2025 **Revised:** 04 December 2025 **Accepted:** 25 December 2025

ARTICLE INFO

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Keywords:
Rare diseases,
Artificial Intelligence,
Genomic Variants,
Variant Interpretation,
Early Diagnosis,
Phenotype Recognition

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ABSTRACT

Rare diseases (RDs) represent a broad category of conditions that individually affect a relatively small proportion of the population but collectively impact millions of people worldwide. Because of their clinical heterogeneity and frequently nonspecific symptoms, obtaining an accurate diagnosis can be a prolonged process, with many patients experiencing years of uncertainty before receiving a definitive diagnosis. Approximately 80% of rare diseases have a genetic basis, and the majority are chronic conditions with limited treatment options. In recent years, Artificial Intelligence (AI) has emerged as a valuable tool for addressing these challenges. Using Machine Learning (ML) and Deep Learning (DL) techniques, AI systems can process and analyze large volumes of genomic, phenotypic, and clinical data, improving both the speed and accuracy of diagnosis. AI-based platforms such as Phenomizer and Face2Gene assist clinicians in recognizing disease-associated phenotypic patterns and prioritizing potential diagnoses. In addition, AI facilitates patient screening using Electronic Health Records (EHRs) and contributes to treatment optimization as well as disease management. Within neonatal medicine, AI is increasingly applied to facilitate the diagnosis of rare diseases through rapid genomic data interpretation, syndrome recognition based on facial features, and screening for inherited metabolic disorders. Despite these advances, several limitations remain, including restricted data availability, concerns regarding data privacy, and the need for greater transparency and trust in AI-driven healthcare applications.

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Introduction

Rare diseases (RDs) are a heterogeneous group of conditions, each affecting a small percentage of the population, yet collectively impacting a significant number of individuals worldwide. The definition varies across regions, and it is estimated that between 6,000 and 8,000 rare diseases have been identified globally[1,2]. Because of their wide range of symptoms and clinical manifestations, diagnosing rare diseases is often complicated and delayed. On average, patients wait more than five years to receive an accurate diagnosis, typically consult around eight different physicians, and may experience two to three misdiagnoses during this process[3].

Approximately 80% of rare diseases are of genetic origin[4]. Most of these disorders are chronic and incurable, persisting throughout an individual's lifetime even when symptoms are not immediately apparent. Furthermore, about 95% of these conditions do not have disease-specific therapies, which is why they are commonly referred to as "orphan diseases"[5].

Artificial Intelligence (AI) refers to the ability of machines to perform tasks that typically require human intelligence, including learning, problem-solving, and decision-making. It is a broad field that includes systems and technologies designed to mimic human cognitive processes[6].

Artificial Intelligence and Machine Learning Concepts

Machine Learning (ML), a branch of AI, utilizes large datasets to identify patterns, improve performance, and make predictions. In medical diagnostics, ML commonly operates through three main types of algorithms[7]: (A) supervised learning, which classifies or predicts outcomes based on labeled examples; (B) unsupervised learning, which identifies hidden patterns in unlabeled data; and (C) reinforcement learning, which develops strategies through reward-and-punishment mechanisms. Deep Learning (DL), a more advanced subset of ML, relies on artificial neural networks and is particularly effective in complex tasks such as image recognition, where intricate problems are decomposed into simpler hierarchical representations[8].

In addition, Natural Language Processing (NLP), another branch of AI, focuses on understanding and interpreting human language. In healthcare settings, NLP is used to extract meaningful information from clinical and medical records[8,9]. (Table 1).

AI's Role in the Detection of Rare Diseases

AI for the Interpretation of Genomic Variants

These technologies provide robust tools for integrating genomic, phenotypic, and clinical data. One of the most impactful applications of AI in rare disease diagnostics is genomic data interpretation. Modern AI platforms can automate variant prioritization by integrating pathogenicity predictions, population frequency data, inheritance patterns, and gene–disease associations simultaneously and in real time[10,11]. For example, platforms such as MOON, Fabric Genomics, Emedgene, and GEM are widely used for genomic variant interpretation. By filtering and ranking candidate variants, these systems can effectively narrow down the number of variants that require further clinician review.

Table 1. Applications of AI and ML in Problem-Solving and Decision-Making Processes (from Reference 8)

	Role	Application
Supervised learning	Uses labeled datasets to classify or predict outcomes	Classifying genetic variants as benign or pathogenic
Unsupervised learning	Identifies hidden patterns in unlabeled datasets	Clustering patients with similar phenotypic features
Deep learning	Processes complex data like images or sequences	Identifying rare disease markers from MRI scans
Natural language processing	Analyzes unstructured text data from EHRs	Flagging potential red flags in medical histories for early diagnosis

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Phenotype-Based Diagnostic Systems

Another important application of AI in rare disease diagnosis involves integrating patient phenotypic features with genomic data to improve diagnostic accuracy. Several automated tools have been developed for this purpose. Phenomizer computes similarity scores between a patient's phenotype set and known Mendelian disorders, thereby narrowing diagnostic possibilities. GEM (Genetic Evaluation Module) combines phenotype scoring with variant pathogenicity assessment to generate ranked diagnostic hypotheses. Phen-Gen integrates sequencing data and phenotypes, improving recognition of both coding and non-coding variants, and demonstrating a reported 52% higher accuracy compared with genotype-only analyses[12]. Similarly, PhenIX and Xrare prioritize genetic variants based on phenotypic characteristics. Face2Gene and DeepGestalt apply deep learning and facial recognition to analyze facial morphology, supporting the identification of syndromic conditions as digital dysmorphologists[13,14]. Additionally, AMELIE mines scientific literature to prioritize candidate genes based on phenotypic relevance and published evidence, linking genomic findings with up-to-date biomedical knowledge[15]. Collectively, these tools streamline variant prioritization, improve diagnostic accuracy, and support clinicians in interpreting complex genomic and phenotypic data.

Screening Based on Electronic Health Records

AI is increasingly used for large-scale patient screening through electronic health records (EHRs). Through machine learning and natural language processing (NLP), both structured and unstructured EHR data can be analyzed. These tools assist in identifying patients who may be at risk for rare diseases. Screening can be conducted retrospectively or prospectively, and studies have shown high levels of accuracy and sensitivity in detecting disorders such as Pompe disease and mucopolysaccharidosis type II (MPS-II)[12,16].

AI in treatment and management

AI also has a key role in the treatment and management of rare diseases. Some AI systems are designed to be adaptive and patient-centered, adjusting therapies to be adjusted according to disease progression and individual patient responses. These systems can identify early signs of diminished treatment effectiveness, monitor clinical outcomes, and integrate both electronic health data and patient-reported information. These systems offer medication reminders, dose adjustments, and pattern recognition of clinical or lab changes[5].

Applications of Artificial Intelligence in Neonatal

In neonatal medicine, artificial intelligence aids the diagnosis of rare diseases through enabling rapid interpretation of genome sequencing data, recognition of syndromes through facial photographs (such as with Face2Gene), and facilitating screening for inherited metabolic disorders[17].

Challenges

Using AI in rare diseases shows considerable promise, but it also presents significant challenges. One major limitation is the data scarcity. Because rare diseases affect relatively few patients, the availability of high-quality datasets is limited, making it difficult to train robust AI models. Efforts such as open data initiatives and patient registries can help address this issue, and techniques such as advanced deep-learning architectures and data augmentation can partially solve this. Another important challenge is the interpretability of AI decisions. Many AI models work like "black boxes," so doctors may not know why a decision was made. In the field of natural language processing, even small differences in wording may lead to inaccurate interpretations. Context-aware models, like transformer-based architectures, can improve performance, although the problem is not fully solved. Privacy concerns also remain significant, as AI systems may uncover unexpected findings that raise questions about informed consent and data sharing.

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Consequently, strict rules are needed to ensure patient protection and the ethical use of data[14].

Conclusion

Despite its potential, the integration of AI in rare disease care faces ethical, legal, technological, and social challenges. Issues such as algorithmic bias, data security, and insufficient regulatory oversight remain critical concerns. In addition, patients often place greater trust in physicians than in AI systems, and healthcare professionals may express concerns about the impact of AI on job security. Enhancing transparency, fairness, and safety will therefore be essential for the responsible implementation of AI in the diagnosis and management of rare diseases.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

The author would like to thank the Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, for its support and encouragement in the preparation of this manuscript.

Funding

This research received no external funding.

Ethical Considerations

This study did not involve human participants or animal subjects. All information used in this review was obtained from publicly available sources; therefore, no ethical approval was required.

Author's Contribution

Melina Bitarafan: Conceptualization, Literature review, Writing – original draft, Writing – review & editing, Visualization (table design), Final approval.

How to Cite: Bitarafan M. AI Applications in Diagnosing Rare Genetic Disorders. World J Peri & Neonatol 2025; 8(1): 26-30.
DOI: 10.18502/wjpn.v8i1.21581

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