Review

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Can Artificial Intelligence be a Trustable Tool for Future Difficult-Treat Diseases?

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Artificial intelligence holds immense promise for combating the world's most difficult-to-treat diseases by analyzing complex biological data, accelerating drug discovery, and personalizing treatments. However, trust remains the central challenge preventing full integration into clinical medicine. For AI to become reliably trusted, it must overcome issues of transparency, bias, fairness, accountability, and clinical validation. Its decisions must be explainable, its training datasets representative, and its performance rigorously proven in real-world settings. Regulatory bodies must establish standards for evolving AI systems, and ethical safeguards must ensure patient agency and equitable outcomes. The future lies not in replacing clinicians but in forming an effective human-AI partnership that enhances decision-making and improves patient care. With careful development and governance, AI could become a dependable tool that transforms the management of complex diseases worldwide.

Keywords: Artificial Intelligence; Difficult-To-Treat Diseases; Medical Trust; Predictive Modeling; Personalized Medicine

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Artificial intelligence is no longer an abstract vision of technological progress or a distant dream of computational cognition; it has become a tangible presence in clinics, laboratories, and global health networks. As humanity faces an era of complex, multi-factorial, and rapidly evolving diseases, the question is no longer whether AI will participate in medicine, but whether it will be trusted to do so (Sagona et al., 2025). Difficult-to-treat diseases—those rooted in genetic complexity, immunologic dysregulation, microbial evolution, environmental stressors, or multidimensional comorbidities—represent some of the greatest challenges modern healthcare must confront. They strain systems, perplex clinicians, and defy conventional drug development strategies. In this context, AI emerges not as a mere supportive tool, but as a potential catalytic force capable of

reshaping how diseases are understood, predicted, and managed (Yadav et al., 2024).

Yet trust is the critical threshold. To integrate AI meaningfully into the future of hard-to-treat disease management, societies must grapple with the philosophical, ethical, and operational conditions under which trust in artificially generated insights can be earned, maintained, and justified. Trust cannot be commanded by technological sophistication alone; trust must be validated through performance, safety, transparency, and alignment with human welfare. This perspective examines whether AI can become a trustable tool in the fight against the most challenging diseases, and under what conditions such trust can be responsibly extended.

The Changing Landscape of Difficult-to-Treat Diseases

Diseases considered "difficult to treat" in the twenty-first century extend far beyond the traditional categories of rare genetic disorders or late-stage malignancies (Dalal, 2025). They include autoimmune conditions shaped by environmental triggers, chronic infections complicated by antimicrobial resistance, metabolic diseases fueled by lifestyle and socioeconomic factors, and neurodegenerative disorders progressing through pathways still not fully understood. These diseases carry layers of complexity that far exceed what linear diagnostic reasoning or traditional biomarker-based classification could easily manage (Harald et al., 2018).

For clinicians and researchers, the challenge is twofold. First, the biological mechanisms underlying many of these conditions are vast, interdependent, and dynamic. Second, their manifestations differ widely between individuals due to genetic variation, epigenetic influences, environmental exposures, and social determinants of health (Minnis et al., 2024). A person's disease, therefore, is not merely the disease itself but an intricate interplay of unique contextual factors. Standardized medical tools often fail to capture this individuality.

AI enters this environment as a force capable of processing complexity at a scale and speed beyond human limits. Machine learning models can detect hidden patterns inside massive genomic datasets, neural networks can interpret imaging with unprecedented nuance, and generative systems can propose hypotheses or therapeutic strategies that might otherwise remain invisible (Sharma et al., 2024). As difficult-to-treat diseases grow in prevalence and complexity, AI's role becomes not only desirable but perhaps essential.

Why AI Holds Transformative Potential

The transformative power of AI lies in its capacity to integrate diverse sources of information into meaningful outputs. Traditional medicine often relies on structured, siloed data: laboratory results, imaging, clinical notes, or individual gene panels (Fahrner et al., 2025). AI, in contrast, can synthesize vast biological, environmental, and behavioral datasets to reveal cross-system relationships that humans cannot easily detect.

One of AI's most powerful contributions is its predictive ability. Rather than simply responding to disease onset, AI systems can forecast an individual's risk trajectory, anticipating complications or treatment failures before they manifest clinically (Siddiqui et al., 2025). This predictive potential is particularly valuable in conditions like autoimmune illnesses, cancers, viral evolution, or neurodegeneration, where early intervention significantly improves outcomes but early detection is notoriously difficult.

Moreover, AI offers unprecedented speed in drug discovery. Traditional drug development is slow and costly, with many promising compounds failing due to unforeseen interactions or insufficient efficacy. AI can screen millions of compounds, simulate protein-ligand interactions, and predict toxicity with remarkable efficiency (Kant et al., 2025). For difficult-to-treat diseases—especially those lacking effective therapies—this acceleration is not merely beneficial; it can be lifesaving.

Furthermore, AI excels at personalization. Hard-to-treat diseases rarely respond well to one-size-fits-all interventions. With AI, treatment plans can be refined to match a patient's molecular profile, lifestyle, immune responsiveness, or drug metabolism patterns (Serrano et al., 2024). Such personalization could redefine chronic disease management and overcome barriers that currently limit the success of many therapies.

The Challenge of Trust in Artificial Systems

Despite its potential, AI remains an uncertain ally in healthcare due to a fundamental issue: trust. Unlike medical tools grounded in centuries of scientific tradition or clinical trials defined by rigorous protocols, AI systems evolve rapidly and often operate through opaque decision-making processes (Göktaş & Grzybowski, 2025). Human clinicians may accept a recommendation from a colleague whose expertise is known and whose reasoning can be interrogated. But when a model produces a result based on millions of parameters shaped by data imperceptible to human cognition, trust becomes far harder to establish.

A major barrier to trust is transparency. Many high-performing AI systems rely on deep learning architectures whose internal logic cannot be easily interpreted (Eschenbach, 2021). Even when such systems demonstrate strong predictive accuracy, the inability to explain how conclusions were reached breeds skepticism. In complex diseases, where treatment decisions carry significant risk, opacity is not acceptable.

Bias presents another threat to trust. AI models learn from the data they are fed; if the data reflect social, genetic, or environmental imbalances, the model may replicate or amplify these disparities (Asan et al., 2020). A tool meant to improve access or accuracy could inadvertently harm vulnerable populations. In difficult-to-treat diseases—many of which disproportionately affect underrepresented communities—this risk is particularly acute.

Additionally, AI systems may be perceived as unreliable when faced with unprecedented scenarios. Rare disease variants, novel pathogens, or unusual patient presentations challenge even the most robust models (Seoni et al., 2023). Human clinicians rely on judgment, context, and empathy to navigate uncertainty; AI, unless designed to manage ambiguity, may fail in unpredictable ways.

Trust also depends on accountability. When a treatment

recommendation leads to harm, who is responsible: the developer, the clinician, the institution, or the AI itself? The absence of clear frameworks for liability undermines confidence in AI-driven care.

Conditions Under Which AI Can Become Trustable

For AI to be a trustable tool in managing difficult-to-treat diseases, it must meet rigorous conditions that prioritize safety, transparency, fairness, and human oversight. First, explainability must advance beyond its current limitations. Clinicians and patients must be able to understand the reasoning behind the AI's outputs, even if the underlying mathematics remains complex (Jha et al., 2025). Tools that visualize decision pathways or highlight meaningful data features can bridge this gap.

Second, AI must be trained on diverse, representative datasets. Datasets should reflect not only demographic diversity but the clinical heterogeneity characteristic of hard-to-treat diseases (Keyl et al., 2025). The inclusion of global data, genetic diversity, and varied environmental exposures is essential. Without this, AI will inherit biases that undermine its reliability and fairness.

Third, AI must undergo rigorous clinical validation. Just as new drugs require trials across phases and populations, AI models intended for clinical use must be subjected to robust evaluation systems (Reis et al., 2021). These evaluations must measure not only accuracy but real-world safety, longitudinal performance, and compatibility with clinical workflows.

Fourth, regulatory frameworks must evolve. Traditional medical regulatory bodies must adapt to the dynamic nature of AI, developing standards that evaluate evolving models, continuous learning systems, and the impact of updates. Without clear rules, trust cannot be institutionalized.

Fifth, AI should be used in a way that makes human judgment stronger, not weaker (Asan et al., 2020). AI should function as an augmentation tool that enhances decision-making by offering insights, predictions, and alternative strategies. Trust grows when clinicians feel empowered rather than threatened by the presence of AI.

Finally, ethical considerations must shape the development environment. Patients must have agency over how their data is used. Developers must commit to transparency, safety, and equitable outcomes (Krishnan et al., 2023). Healthcare institutions must embrace accountability frameworks that clearly delineate responsibility.

The Human-AI Partnership as the Future of Disease Management

The future of difficult-to-treat disease management will likely belong not to AI alone, but to a partnership between human intelligence and artificial systems. Human clinicians excel in empathy, contextual reasoning, ethical judgment, and the integration of social and emotional factors into care—areas where AI remains limited (Krishnan et al., 2023). AI, on the other hand, excels in processing massive datasets, recognizing subtle patterns, and offering predictive insights at scales beyond human capacity.

The most promising vision is one where AI becomes a constant companion in clinical reasoning, enriching human understanding with computational depth. For complex diseases requiring multidisciplinary care, AI can unify diverse data streams, coordinate treatment pathways, and highlight early signs of deterioration (Altucci et al., 2025). In research settings, AI can accelerate discovery by offering hypotheses, modeling interactions, and identifying promising therapeutic directions.

In low-resource settings, AI could become a critical equalizer, offering diagnostic or predictive support in environments lacking specialist expertise (Fahim et al., 2025). This could dramatically change outcomes in diseases often left untreated or misdiagnosed due to resource limitations.

Most importantly, a trusted AI system could restore time to clinicians. By reducing administrative burdens and offering structured insights, AI frees clinicians to focus on the interpersonal, ethical, and compassionate dimensions of care. Trust, therefore, emerges not from replacing human roles but from enhancing human capacity.

A Cautious but Optimistic Future

The possibility that AI could become a trustable tool for future difficult-to-treat diseases is both plausible and promising, but not guaranteed. The technology is advancing rapidly, often outpacing the ethical, regulatory, and clinical structures required to support it (Anderson & Sutherland, 2024). To ensure trust, society must invest as heavily in governance, transparency, and fairness as it does in computational power and algorithmic innovation.

If AI is developed responsibly—guided by ethical principles, validated through rigorous science, and integrated into human-centered medical environments—it may become one of the most transformative tools in the history of medicine (Krishnan et al., 2023). Its capacity to model complexity, personalize interventions, and accelerate discovery aligns perfectly with the demands of diseases that defy conventional management.

The path forward requires humility, caution, and collaboration. Trust must be earned through evidence and maintained through accountability. But if these conditions are met, AI may become not only a trusted ally but an indispensable force in confronting the most difficult diseases humanity will face.■

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